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Therapeutic Recommendations for the Management of Older Adult Patients with Sjögren's Syndrome

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Abstract

Primary Sjögren's syndrome (SjS) is a systemic autoimmune disease most commonly diagnosed in middle-aged women. Although the disease can occur at all ages, it is diagnosed between 30 and 60 years of age in two-thirds of patients. In more than 20% of cases, the people are older than 65 years. In this review, we focus on the therapeutic management of primary SjS in older patients, following the recently published 2020 European League Against Rheumatism (EULAR) recommendations for the management of the disease with topical and systemic therapies. These recommendations are applicable to all patients with primary SjS regardless of age at diagnosis, although the therapeutic management in older patients requires additional considerations. Older patients are more likely to have pulmonary, liver, kidney, or heart-related comorbidities (even cognitive disturbances); caution is required when most drugs are used, including muscarinic agents, systemic corticosteroids and synthetic immunosuppressants. It is also important to monitor the use of eye drops containing steroids due to the increased risk of developing cataracts, a frequent ocular complication in the older population. In contrast, the majority of drugs that can be used topically (pilocarpine rinses, eye drops containing topical non-steroidal anti-inflammatory drugs (NSAIDs) or cyclosporine A, topical dermal formulations of NSAIDs) have shown an acceptable safety profile in older patients, as well as rituximab. A rigorous evaluation of the medical history of older patients is essential when drugs included in the EULAR guidelines are prescribed, with special attention to factors frequently related to ageing, such as polypharmacy, the existence of organ-specific comorbidities, or the enhanced susceptibility to infections.

1 Introduction

Primary Sjögren's syndrome (SjS) is a systemic autoimmune disease with a wide clinical spectrum that extends from sicca symptoms of the mucosal surfaces to extraglandular manifestations. Exocrinopathy, the hallmark of the disease, often results in dryness of the mouth and eyes, fatigue, and joint pain. These three symptoms occur in > 80% of patients with this disease and have a considerable effect on quality of life, primarily due to disabling fatigue and associated loss of work productivity. An overlap between SjS and systemic autoimmune diseases is common in daily clinical practice

[1]. Disease predominantly affects middle-aged women, but can also be observed in children, men and the elderly [2]. The incidence of primary SjS ranges between 3 and 11 cases per 100,000 individuals [3, 4], whereas the prevalence ranges between 0.01% and 0.72% [5, 6]. Beyond sicca syndrome, primary SjS may be a serious disease, with an excess of mortality mainly due to systemic disease and haematological cancer. The variable presentation often linked to the influence of multiple factors may result in diagnostic delays of up to 10 years with patients often visiting various specialists [7].

In older patients, clinical presentation of primary SjS can be atypical, and in some cases, it is difficult to distinguish primary SjS from SLE-SjS or systemic lupus erythematosus (SLE). Especially in older adults, besides other autoimmune diseases, several conditions may increase sicca complaints: dehydration, polypharmacy, chemotherapy, and head and

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Key Points

Dryness of the eyes and mouth (the key symptoms of Sjögren's syndrome [SjS]) are reported by up to 30% of persons aged > 65 years, particularly in perimenopausal and postmenopausal women.

Older SjS patients have an increased risk of polypharmacy that may contribute to worsening glandular dysfunction causing more complicated oral and ocular dryness.

Therapeutic options may include symptom-relieving products and lifestyle changes.

All treatment options need to be carefully adapted to the individual situation of the patient to reduce symptoms, avoid complications, and improve their quality of life.

neck radiation [8, 9]. Moreover, with age, inadequate tear production is common, salivary secretion may reduce and salivary composition may undergo chemical changes [8]. Furthermore, malnutrition and diabetes mellitus play a role in hyposalivation and are more frequent in older patients [8, 10]. Impaired cholinergic stimulation of muscarinic salivary receptors may lead to xerostomia in older adults as well [8, 11, 12]. It is essential to recognize the difference between xerostomia, the subjective patient-reported symptom of having a dry mouth, and salivary gland hypofunction, reduced salivary flow measured by quantifying the amount of saliva produced at a given time. Xerostomia affects the patient's speech, eating, taste, swallowing, and wearing dentures. Dentally, xerostomia increases incidence of caries and can also contribute to halitosis and even a burning sensation in the mouth [13]. The most typical clinical signs associated with hyposalivation are dysgeusia, dysosmia, dental caries, candidiasis, periodontal disease, gland inflammation, mucositis and oral ulcers. Older patients with primary SjS, compared with younger ones, have a lower frequency of serologic abnormalities such as anti-SSA, anti-SSB, rheumatoid factor and hyperglobulinemia [14]. Parotid gland involvement is observed less frequently in older patients > 70 years of age than in those < 70 years of age, and older patients also have a higher frequency of pulmonary involvement and involvement of the peripheral nervous system [2, 15].

In this review, we focus on the therapeutic management of primary SjS in older patients (see Box 1 for methodology)

following the recently published 2020 European League Against Rheumatism (EULAR) recommendations for the management of the disease with topical and systemic therapies [16].

2 General Recommendations

The EULAR Task Force endorsed the presentation of three overarching, general consensus-based recommendations for patients with primary SjS, that included the management at, or in close collaboration with, centres of expertise using a multidisciplinary approach; the recommendation that the first therapeutic approach to dryness should be symptomatic relief using topical therapies; and that the use of systemic therapies may be considered for the treatment of active systemic disease. These general recommendations are applicable to all SjS patients regardless of age at diagnosis.

3 Management of Sicca Symptoms

It is especially important to investigate other common causes of hyposalivation and dry eyes (Tables 1, 2) and the use of concomitant medications in the older population, since many pharmacologic agents produce oral and ocular dryness (Tables 3, 4). Preventive measures such as avoiding sugar or medications which are known to cause dry eye or mouth, and regular dental and ophthalmologic check-ups are recommended.

3.1 Management of Oral Dryness

The EULAR Task Force recommended a baseline evaluation of salivary gland function before and after starting treatment for oral dryness, with a therapeutic approach driven by the results obtained in the measurement of salivary glandular function and not driven by the patient's subjective feelings. One of the major challenges to this special field is the identification and screening of patients with xerostomia, which is complex. Screening tools must be able to identify the diagnosis of xerostomia, which can be objectively evaluated by unstimulated whole salivary flows and stimulated whole salivary flows using sialometry, which consists of collecting saliva to measure the amount of secretion produced per minute [17, 18]. Hyposalivation is considered for flows of < 0.1 mL/min for non-stimulated saliva and < 0.7 mL/min for stimulated saliva [19]. It can also be assessed by directly questioning individuals [20] or using the Xerostomia Inventory, a multi-item instrument for measuring xerostomia symptoms that enables an estimate of their severity to be made on a continuous scale [21]. A dental and periodontal examination to assess oral health should be made every

Table 1 Causes of hyposalivation other than Sjögren's syndrome

Drugs (see Table 3)
Recreational drug use: marijuana use
Bacterial and viral infections
Dehydration
Psychogenic causes (depression, anxiety)
Ageing
Systemic diseases
Granulomatous diseases (sarcoidosis, tuberculosis, leprosy)
Amyloidosis
Cystic fibrosis
Poorly controlled diabetes mellitus
Chronic sclerosing sialadenitis (IgG4-related sialadenitis)
Lymphoma
Head and neck irradiation
Head or neck trauma or surgery
Absence or glandular malformation

Table 2 Causes of dry eye symptoms other than Sjögren's syndrome

Drugs (see Table 4)
Tear composition disturbance
(a) Mucinous component deficiency
Stevens-Johnson syndrome, pemphigoid
Chronic conjunctivitis
Toxicity
Hypovitaminosis A
(b) Aqueous component deficiency
Congenital absence or glandular malformation
Trauma
Neurological disorder
(c) Lipid component deficiency
Chronic blepharitis/meibomitis
Congenital absence or glandular malformation
Tear film disturbance
Neurological disorder
Symblepharon
Corneal surface disturbance
Corneal anaesthesia
Epithelial irregularity

3–6 months [22]. When we apply these recommendations to older SjS patients, it is useful to know how salivary gland function may be affected by the age of the patient. Unfortunately, there are no studies focused on evaluation of salivary gland function in older SjS patients in comparison with younger patients, but we have selected some manuscripts analysing function in non-SjS populations (Table 5). Several studies have analysed the features that can influence a change in saliva production in older adults. The key factor

Table 3 Drugs associated with dry mouth syndrome

Hypnotics and sedatives
Narcotics
Muscle relaxants
Antidepressants and anxiolytics
Antiparkinson drugs
Antihistamines
Diuretics
Antihypertensives: α -blockers, β -blockers
Antiarrhythmics
Anticholinergics: atropine
Nasal decongestants
Amphetamines

Table 4 Drugs associated with dry eye syndrome

Antihistamines and decongestants
Selective, non-sedating H1 receptor antagonists
Non-selective H1 receptor antagonists
Decongestants
Antidepressants
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Serotonin–norepinephrine reuptake inhibitors
Monoamine oxidase inhibitors
Noradrenergic and specific serotonergic antidepressants
Norepinephrine-dopamine reuptake inhibitors
Serotonin antagonist and reuptake inhibitors
Norepinephrine reuptake inhibitors
Selective serotonin reuptake enhancers
Norepinephrine dopamine disinhibitors
Anticonvulsants
Antipsychotic drugs
Antiparkinson drugs
β -Blockers
Non-selective agents
β 1-Selective agents
Miscellaneous medications
Antispasmodics
Gastroprotective agents
Antiemetics
Nonsteroidal anti-inflammatory drugs
Respiratory system drugs
Opiates
Antiarrhythmic agents
Antihypertensive agents
Antithyroid agents
Antineoplastic agents
Antiviral agents
Anaesthetic adjunct medications
Drugs used for urinary incontinence

influencing salivary flow rate was age. All studies except one (one small study comparing two groups of 14 patients [23]) reported a reduced salivary flow rate in older people versus young people, mainly using ages > 65 or 70 years as the cut-off [24–28]. One study reported lower salivary flow rate in people aged 86 years in comparison with those aged 76 years, despite the use of drugs in general [24]. Whole salivary flow rate and submandibular and sublingual salivary flow rate were significantly reduced in older people, both in unstimulated and stimulated conditions [26]. In healthy older adults, parotid flow is usually unchanged. There are, however, some changes in the submandibular flow, particularly when these glands are stimulated for a long time or a minimal stimulus is applied (mostly due to an effect of the increasing use of drugs in older adults). Sex also may influence salivary flow rate, and one study reported that the salivary flow rate for women was 40% lower than for men [29]. The use of concomitant medications was also closely related to a reduced salivary flow rate and unstimulated whole salivary flows [27], especially in patients using two or more hyposalivatory drugs [29], or with coexisting diabetes mellitus, since subjects with diabetes had significantly lower stimulated parotid flow rates than nondiabetic control subjects [30]. Older age and male sex have also been associated with a higher rate of root caries [31].

Based on the results obtained in measuring salivary gland function, two mechanisms may be used to initiate the therapeutic approach to oral dryness: salivary gland stimulation (non-pharmacological or pharmacological) and saliva substitution. Therefore, the preferred first therapeutic approach for oral dryness according to salivary gland function will be non-pharmacological stimulation in patients having mild salivary gland dysfunction, pharmacological stimulation for those with moderate dysfunction and the use of saliva substitution in patients showing a severe salivary gland dysfunction. As general recommendations, patients should be encouraged to drink water, avoid alcohol and tobacco and decrease their intake of food and drinks that may promote xerostomia or caries (e.g. those that are caffeinated or contain sugar) [32]. Patients should be counselled to practice oral hygiene and brush teeth at least twice daily including before bed at night using specific pastes and mouthwashes for dry mouth, usually containing no lauryl sulfate, which is the detergent for toothpastes, as this ingredient usually irritates and removes the patient's residual saliva. Although patients should be encouraged to drink water, it is important to mention that water at such is not a good moistener of the oral mucosa. The oral mucosa is temporarily moistened, which feels great for patients, but unfortunately will be dry again soon [33]. Moreover, medication-induced dry mouth is a symptom that should not be treated independently in older patients; instead, it should be treated with a multidisciplinary approach that takes into account all potential influencing

factors, including treatments needed for any other oral symptoms. The concept of interdisciplinary preventive care should be adjusted to the patient's individual needs and should focus on all relevant oral symptoms in order to avoid high-risk impairments in oral health, thus delaying the cycle of malnutrition, social isolation, care dependency and frailty that tends to affect the older population.

3.1.1 Non-pharmacological Stimulation

In SjS patients with mild glandular dysfunction, the EULAR Task Force recommended non-pharmacological glandular stimulation as the preferred first-line therapeutic approach, using gustatory stimulants (sugar-free acidic candies, lozenges, xylitol) and/or mechanical stimulants (sugar-free chewing gum) [16]. There are no studies published that specifically studied these stimulants in older primary SjS patients. Any chewing gum or candy used to induce salivation should be sugar-free [32].

Sugar-free chewing gum can be used as a mechanical salivary stimulant after meals to accelerate the clearance of dietary substances and microorganisms, and to promote buffers that neutralize plaque acids and supply antibacterial substances. This approach may improve saliva function in patients with low flow rates, like older patients suffering from xerostomia, or provide symptomatic relief from dry mouth. However, chewing gum is often not well tolerated in people who wear dentures.

Malic acid produces a sour-tasting gustatory stimulus. Its mechanism of action is linked to dissociation of H^+ in malic acid in water, which becomes hydronium ions (H_3O^+); this reaction generates a stimulation of salivary secretion to dilute the concentration of acids in the oral cavity. Xylitol does not stimulate saliva but it reduces erosion and cariogenic potential. Thus, a spray containing malic acid with xylitol seems to be a safe topical sialagogue [34].

3.1.2 Pharmacological Stimulation

In primary SjS patients with moderate salivary gland dysfunction, pharmacological stimulation with muscarinic agonists may be considered, and two drugs (pilocarpine and cevimeline) are licensed for the treatment of oral dryness. Age-related changes in drug metabolism and elimination are important to consider when prescribing muscarinic agonists to patients aged > 65 years, mainly because of a potential for increased risk of adverse effects and toxicities (older patients are more likely to have age-related pulmonary, liver, kidney, or heart-related diseases as comorbidities, which may require caution when these drugs are used. According to the pilocarpine prescription data sheet, adverse events reported by people aged > 65 years and those < 65 years were comparable except for notable trends for urinary frequency, diarrhoea

Table 5 Selected studies evaluating salivary gland function in older patients: baseline and stimulated salivary flow rates, and influence of medications on hyposalivation

Study	Patients (females)	Mean age (y)	Disease/condition	Design	Influence of age in outcomes
Handelman et al. (1989) [29]	157 (130)	86.6 (SD $\pm$ 5.6)	Residents of an intermediate care facility 71% were taking one or more drugs	Observational	Age and dentition were unrelated to any of the hyposalivation indicators
Närhi et al. (1992) [24]	368 (263)	79	Healthy	Prospective	Number of medications used daily was higher in 86-year-olds than in the two younger age groups ($p < 0.01$) Unmedicated subjects: 76-year-olds had higher SWSF than the 81-year-olds ($p < 0.05$) SWSF was higher in the medicated 76-year-olds than in the medicated 86-year-old subjects ($p < 0.05$) Differences among the three age groups in the use of anticholinergic drugs ($p < 0.001$)
Kagami et al. (1995) [27]	20 (13)	61 (16–81)	Sicca syndrome	Case series	Maximum RI count: ≤ 65 -year-old vs ≥ 65 -year-old patients only in the submandibular gland ($p < 0.05$) Mean USWS volume in the ≥ 65 -year-old group vs the ≤ 65 -year-old group ($p < 0.05$) USWS reduction in the medicated patients
Närhi et al. (1998) [31]	183 (127)	79.3	Digestive diseases ($n = 6$) and circulatory diseases ($n = 5$) Subjects with general medication ($n = 13$) Subjects using medication that reduced their salivary secretions ($n = 10$) Healthy	Population-based	Reduced mean secretory velocities of the submandibular gland (≥ 65 y vs < 65 y; $p < 0.05$) Root caries occurred in 40% of 76-year-olds vs 65% of 81- to 86-year-old people ($p = 0.06$) No gender-related differences observed between number of teeth and number of medications used daily according to the age of the subjects Mean number of decayed teeth was highest among the oldest participants ($p = 0.05$)
Fischer and Ship (1999) [23]	28 (14)	Older adults: 68.1 ($n = 14$)	Healthy and unmedicated	Prospective	USWS and SWSF were similar at each time point in younger and older subjects, and remained stable over the collection period
Chávez et al. (2001) [30]	39 (20)	≤ 71 ($n = 17$) > 71 ($n = 22$)	Subjects with DBT ($n = 29$ at baseline; $n = 24$ at 1 year)		NE

Table 5 (continued)

Study	Patients (females)	Mean age (y)	Disease/condition	Design	Influence of age in outcomes
Affoo et al. (2015) [26]	NE	Young subjects: 15–59 Older adults: 60–97	Healthy or generally healthy	Meta-analysis 47 studies were included	Lower WSPR in the elderly group ($p < 0.001$) Lower SMSL SFR in the elderly group ($p < 0.001$)
Smith et al. (2013) [25]	540 (270)	Young: 20–30; Middle-aged: 40–50; Older ≥ 70 Young: $n = 180$ (90) Middle-aged: $n = 180$ (90) Older: $n = 180$ (90)	Healthy individuals (aged 20–97)	Cross-sectional design	Lower rate of saliva production in the older group (mean 2.08) in comparison with the younger (mean 4.43) and the middle-aged (mean 4.27) groups Saliva weight: difference between the young and older participants ($p < 0.001$) Saliva weight: difference between the middle-aged and older participants ($p < 0.001$)
Iwasaki et al. (2018) [28]	600 (294)	70	Community-dwelling Japanese adult	Prospective	Low SWSF tertile was associated with all-cause mortality in men (vs high SWSF tertile: aHR 2.05; 95% CI 1.01–4.17)

aHR adjusted hazard ratio, DBT diabetes mellitus, F female, NE not specified, NS not significant, RI radioisotope, SD standard deviation, SFR salivary flow rate, SMSL submandibular and sublingual, SWSF stimulated whole salivary flow rate, USWS unstimulated whole salivary flow rate, WSPR whole salivary flow rate

and dizziness, with the incidences of urinary frequency and diarrhoea being about double and the incidence of dizziness about three times as high in older compared with non-older patients [35]. Unfortunately, very few studies have tested these drugs in older populations with xerostomia and none in older primary SjS patients (Table 6). With respect to pilocarpine, a crossover study in patients with advanced cancer with xerostomia (mean age of 71 years) compared a mucin-based artificial saliva with pilocarpine hydrochloride and found that pilocarpine was more effective in terms of mean change in visual analogue scale scores for xerostomia although with a significant higher frequency of adverse events (24% withdrew from the study, mainly for sweating and dizziness) in comparison with patients treated with artificial saliva [36]. Another study randomized 40 older patients (all but three aged > 65 years) to receive pilocarpine mouthwash or water rinse (control group) and reported that visual analogue scale scores were significantly reduced after pilocarpine mouthwash treatment, with a higher overall improvement (47% of the pilocarpine group compared with 14% of the controls; $p < 0.05$) and with increased stimulated salivary flow rate (0.71 to 0.83 mL/minute; $p < 0.05$) after pilocarpine mouthwash treatment. Five of 24 patients reported side effects after pilocarpine mouthwash use, but these were predominantly limited to oral discomfort, suggesting that their administration as mouthwash could be useful and probably safer than their oral administration in older patients [37].

3.1.3 Saliva Substitution

It is preferable to consider saliva substitution as the therapeutic approach to alleviate symptoms in patients with severe glandular dysfunction (poor or no residual glandular function). In such patients, the salivary glands cannot be stimulated by either pharmacological or non-pharmacological interventions. The ideal preparation is one with a neutral hydrogen potential (pH), containing fluoride and other electrolytes, which imitates the composition of natural saliva; saliva substitutes are commercially available in the form of oral sprays, gels and rinses [16]. There are no studies evaluating gels/saliva substitutes in older primary SjS patients, and very few in older patients with xerostomia (Table 7). Some studies have reported a subjective better effect of Saliva Orthana and MAS 84 in comparison with water [38]. In addition, the effectiveness and acceptability of a saliva substitute product (Biotene) in the treatment of xerostomia in 20 older patients revealed significant improvements in the number and severity of symptoms between the pre-test and the post-test groups [39], while a pre-post design conducted in 118 older patients (mean age 71 years) found that the use of oral moisturizing jelly for 2 weeks significantly reduced symptoms of dry mouth, while the use for 1 month reduced the signs of xerostomia, prevented the

Table 6 Controlled trials and prospective studies evaluating the use of pilocarpine in older people presenting with xerostomia

Study	Patients	Mean age (y)	Disease/condition	Design	Drug	Variables and significant differences
Davies et al. (1998) [36]	70	71 (42–89)	Advance cancer	Prospective	Pilocarpine	VAS for xerostomia: pilocarpine more effective than artificial saliva ($p=0.003$) More side effects with pilocarpine vs artificial saliva ($p<0.001$)
Tanigawa et al. (2015) [37]	40	71.5 $\pm$ 4.7	Xerostomia	RCT	Pilocarpine mouthwash ($n=19$)	VAS scores were reduced after pilocarpine mouthwash ($p<0.05$) Overall improvement: pilocarpine group 47% vs 14% control group ($p<0.05$) SWSF increased after pilocarpine mouthwash ($p<0.05$)

RCT randomized control trial, SWSF stimulated whole salivary flow, VAS visual analogue scale

decline of salivary pH(s) and improved buffering capacities [40]. Although the scientific evidence is very limited, these studies suggest that the use of saliva substitutes in elderly patients with xerostomia seems safe and effective and should also be recommended in the older subset of primary SjS patients. A Cochrane systematic literature review evaluated the effectiveness of topical treatments for any-cause dry mouth (including SjS) in parallel and cross-over randomized controlled trials using lozenges, sprays, mouth rinses, gels, oils, chewing gum and/or toothpastes and found no strong evidence supporting any one specific topical therapy as more effective in treating dry mouth [16]. However, a recent study has assessed saliva substitutes on their lubricity and related this to their ability to interact with salivary conditioning films, finding that the majority of saliva substitutes did not adsorb on the salivary conditioning films and thus did not enhance lubrication. Only saliva substitutes containing carageenan, carboxymethylcellulose, pig gastric mucin, xanthan gum and carbomer performed better in enhancing oral lubrication [41]. With regard to the prescription of saliva substitutes in general practice, it is wise to prescribe or try a spectrum of saliva substitutes in the individual patient and evaluate with the patient what particular substitute helps that patient best.

3.1.4 Prevention of Dental Caries with Fluoride Mouth Rinses or Neutral Fluoride Gels

Caries at the cervical (root caries) and smooth surfaces of the teeth are typical signs of caries related to a reduced salivary secretion. Dry mouth can have a severe impact on caries risk because the salivary protective system (including salivary buffers, antimicrobial activity, and calcium and phosphate replenishment) is reduced [42]. In patients with a high risk of developing caries, increasing their exposure to fluoride can help to arrest the progression of caries and prevent the formation of new lesions. Adult patients with

this condition have been recommended to use 5000 ppm of fluoride toothpaste twice a day and apply fluoride varnish every 3–6 months [43]. Another protocol is to use 0.09% fluoride rinse daily, followed by the application of 1.23% fluoride gel by a professional every 3–6 months. However, the rinses are not as easy for frail older adults and persons with special needs to use because patients with cognitive deficits may swallow it and patients with physical deficits may find it difficult to swish and spit the rinse. In addition, the gel must remain in patients' mouths for 4 min, which is hard for this population to achieve [13].

3.2 Management of Ocular Dryness

The EULAR Task Force recommended the use of artificial tears and ocular gels/ointments as the first-line therapeutic approach to ocular dryness. Noted age-related changes of the lacrimal gland that contribute to an inadequate tear production include lacrimal gland dysfunction, diminished corneal sensation, altered reflex secretion or the inflammatory destruction of lacrimal glands. The combination of eyelid positioning, abnormal corneal sensation and decreased blink reflex contribute significantly to rapid tear film break-up, and evaporation contributes to age-related dry eye. Inflammation and oxidative stress, which tend to worsen with age, may also play a key role in the development of dry eye among the older population. Older men and women are nearly twice as likely to suffer from dry eyes than their younger counterparts [44]. Dry eye among persons 65 years and older is a multifactorial disease with a broad spectrum of severity. The tear film comprises three main layers: the lipid layer secreted by the meibomian glands, the aqueous layer produced by the lacrimal gland and the mucin layer secreted by conjunctival goblet cells. The loss of normal function of any of these structures resulting from disease trauma or the environment may cause dysfunction of the tear film, producing symptoms of dry eye, such as grittiness, burning and blurred vision.

Table 7 Controlled trials and prospective studies evaluating gels and saliva substitutes in older people with xerostomia

Study	Patients	Mean age (y)	Disease/condition	Design	Drug	Variables and significant differences
Olsson and Axéll (1991) [38]	6	73	Xerostomia SjS ($n=3$) Non-specific sialoadenitis ($n=3$)	Double-blind trial	CMC (MAS 84) and mucin (Saliva Orthana)	Saliva substitutes showed changed friction values around 15 min Both water and the two saliva substitutes relieved the symptoms of dry mouth to some extent They did not have a sufficient long-lasting effect
Matear and Barbaro (2005) [39]	20	65	Xerostomia	Prospective	Saliva substitute product (Biotène)	Post-treatment lower scores for both overall dryness and daytime dryness ($p < 0.01$) Number of symptoms dropped to 2.8 post-treatment ($p < 0.001$) Severe xerostomia: score reduced from 5 to 3.6 ($p = 0.014$) after using Biotène products Moderate to mild xerostomia: score reduced from 3.2 to 2 ($p = 0.046$) after using Biotène products Mouth less dry often after using Biotène products ($p < 0.001$) Mouth less dry at night and when awakening ($p = 0.01$) Mouth less dry during the day ($p = 0.001$) Lower need to sip liquids to aid in the swallowing of dry food ($p = 0.004$)
Dalodomo et al. (2016) [40]	118	71.22 ± 6.8	Hypertension and/or diabetes mellitus	Prospective	OMJ	Decreased average subjective dry mouth scores after using OMJ ($p < 0.0001$) 16% reduction in objective dry mouth scores after using OMJ for 1 month ($p < 0.0086$) Improvement in salivary pH(s) during the OMJ use period in comparison with non-use period ($p = 0.0015$) Better salivary buffering capacity during OMJ use period in comparison with non-use period ($p = 0.035$) Average SFR after the use of OMJ for 2 weeks and 1 month: 0.69 ± 0.53 mL/min and 0.75 ± 0.57 mL/min, respectively ($p = 0.2782$)

CMC carboxymethylcellulose, OMJ oral moisturizing jelly, pH hydrogen potential, SjS Sjögren's syndrome, SFR salivary flow rate

First-line treatment for ocular dryness to supplement the deficient tear film for ocular comfort and adequate vision should be artificial tears and ocular gels, the main ingredients of which are lubricants with a polymeric base or viscosity agent (methylcellulose, hyaluronate); the purpose of this is to add volume to the tear lake, thus increasing the time during which the artificial tears remain on the surface of the eye, and cushioning it to reduce friction between the lid and the globe [16]. Good lid hygiene is also important for tear film health.

Patients with refractory or severe ocular dryness should be managed by an ophthalmologist with substantial experience in corneal disease, wherever possible using topical immunosuppressive-containing drops and serum eye drops. According to the EULAR recommendations [16], refractory ocular dryness is defined as patients who do not improve after using the best-available standard of care (defined as the maximum use of artificial tears and ointments according to the previous recommendation) after ruling out other SjS-unrelated ocular processes (i.e. blepharitis), while severity should be defined according to the results obtained in a specific ophthalmological evaluation of corneal damage by measuring the Ocular Staining Score, together with patient symptoms as assessed by the Ocular Surface Disease Index [16]. In older patients, polypharmacy and diabetes mellitus are very frequent conditions that have been associated with severe ocular symptoms, especially in patients with post-traumatic stress disorder or depression using selective serotonin reuptake inhibitors [45], or in diabetic patients having poorer glycaemic control [46] (Table 8).

3.2.1 Artificial Tears and Ophthalmic Ointments

Standard-of-care therapy with artificial tears can be effective in the older population. Among the extensive literature testing different formulations of artificial tears in patients with conditions related to dry eye (SjS, keratoconjunctivitis sicca, dry eye disease) and dysfunctional tear syndrome, few have

been carried in older populations (Table 9). A prospective case-control study (patients with dry eye vs healthy controls, mean age 65 years) showed that ocular lubricants containing hydroxypropyl methylcellulose may help to maintain physiological corneal density [47], while another case-control study in patients with moderate-to-severe dry eye (mean age 67 years) showed that artificial tears containing carmellose 0.5% and hyaluronic acid 0.1% allowed better stabilization of the tear film in comparison with normal saline artificial tears [48]. However, many of the artificial tear products, though affordable, contain preservatives, including benzalkonium chloride (BAK). With increased susceptibility to tear film instability, loss of goblet cells, and poor epithelial healing from oxidative stress in the ageing population, the addition of preservatives can potentially exacerbate patient symptoms, and as for the SjS general population, preservative-free artificial tears may therefore be better alternatives for older adults, although these do come at an increased cost [49].

Ophthalmic ointments are thicker than artificial tears and may be used to provide symptom control overnight; they are typically used before bedtime because they produce blurred vision and their use should be followed by morning lid hygiene to prevent blepharitis [16, 50]. Unfortunately, no studies or specific subgroup analyses focused on older primary SjS patients have been published and we recommend following the general EULAR recommendations.

3.2.2 Topical Ocular NSAIDs/Corticosteroids

Topical ocular non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids may be prescribed by ophthalmologists as a short-term therapeutic approach (maximum 2–4 weeks), as adverse events may occur with continued use of topical NSAIDs (corneal-scleral melts, perforation, ulceration and severe keratopathy) or topical corticosteroids (infections, increased intraocular pressure and worsening/development of cataracts) [16, 50]. Only one small

Table 8 Prospective studies evaluating the influence of age on the results of ocular tests and requirement of ocular lubrication in elderly people with dry eye disease

Study	Patients	Mean age (y)	Disease/condition	Design	Influence of age on outcomes
Kaiserman et al. (2005) [46]	5,336	70.9 ± 0.13	Diabetic patients	Prospective	Significant difference between diabetic and nondiabetic patients aged 60–89 years who were frequent users of ocular lubrication Association between the amount of ocular lubrication consumed and HbA1c levels ($t = 1.940$; $p < 0.05$), age ($t = 5.034$; $p < 0.0001$) and gender ($t = 3.28$; $p = 0.001$)
Fernandez et al. (2013) [45]	248	69	DES, post-traumatic stress disorder and depression	Prospective	Age was not a predictor of a symptom-based diagnosis of DES (OR 0.99, 95% CI 0.96–1.03; $p = 0.75$)

CI confidence interval, DES dry eye syndrome, HbA1c glycosylated haemoglobin, OR odds ratio

Table 9 Controlled trials and prospective studies testing different formulations of artificial tears (hydroxypropyl methylcellulose, carmellose 0.5% and hyaluronic acid 0.1%) in older people with different diseases and conditions related to dry eye

Study	Patients	Mean age (y)	Disease/condition	Design	Drug	Variables and significant differences
Wegener et al. (2015) [47]	49	67	KCS	RCT	HPMC (<i>n</i> = 49)	Corneal density: reduced in dry eye patients versus controls (<i>p</i> = 0.001) Corneal density: viscous agents were better than carbomer as lubricating agent Carbomer group has corneal density reduction in layers 1 and 2 compared with the control group (<i>p</i> = 0.02; <i>p</i> = 0.007) Corneal density reduction in the povidone group in comparison with the HPMC and control groups (NS)
Vandermeer et al. (2018) [48]	19	67 (± 13.5)	KCS	Prospective	Carmellose 0.5% and hyaluronic acid 0.1% (OF, Allergan) Single blind mode: the patient being his own control A 'control' eye: physiological serum and a 'tested' eye: OF	Variation between initial and 2-hour OSI (0.363 vs 0.204; <i>p</i> < 0.05) Average slope of OSI (0.04 vs 0.01; <i>p</i> < 0.05) Number of blinks (4.2 vs 2.8; <i>p</i> < 0.05) 65% of patients preferred OF 24% did not have a preference 11% preferred normal saline

HPMC hydroxypropyl methylcellulose, KCS keratoconjunctivitis sicca, NS not significant, OF Optive Fusion®, OSI Ocular Surface Index, RCT randomized control trial

Box 1 Literature review methodology

A review of the literature search for the MESH terms “elderly” AND “Sjögren” combined with the terms “management”, “treatment”, “ocular tests”, “corneal staining”, “test de Schirmer”, “Break up time”, “artificial tears”, “ophthalmic ointments”, “plug”, “serum tear drops”, “salivary flow test”, “scintigraphy”, “ultrasonography”, “saliva substitutes”, “gum”, “sodium fluoride”, “saliva substitute”, “oral gel”, “chlorhexidine/xylitol”, “polyacrylic acid”, “carboxymethylcellulose”, “chronic pain”, “musculoskeletal pain”, “aerobic exercises”, “physical activity”, “fatigue”, “immunosuppressive”, “biological”, “abatacept”, “acetaminophen”, “azathioprine”, “belimumab”, “cevimeline”, “cyclophosphamide”, “cyclosporine”, “hydroxychloroquine”, “leflunomide”, “methotrexate”, “mycophenolate mofetil”, “NSAIDs”, “pilocarpine”, “plasma exchange”, “rituximab”, “glucocorticoids”, “tocilizumab”, “tofacitinib” and “lymphoma” was performed using PubMed and MEDLINE databases with the following restrictions: date (1 January 1990 to 31 May 2020), studies (humans) and age (older adults). Additional databases, such as EMBASE and Cochrane Central Library, were also checked

case-control study has been carried out in older patients with SjS (mean age 68 years) comparing ocular tears containing diclofenac sodium 0.1% with tears containing sodium chloride 5% ophthalmic solution. Patients using diclofenac sodium tears showed statistically greater improvement at days 7 and 14, and no significant difference on day 28 than patients using sodium chloride tears. Patients treated with diclofenac 0.1% showed a significantly greater improvement than did the group treated with sodium chloride 5% solution for itching, ocular pain and foreign-body sensation. No

significant adverse effects were observed in either groups, with only self-limited burning and stinging ocular sensations related to instillation of tears [51]. For patients with dry eye accompanied by redness, blepharitis, significant tarsal changes or ocular allergy, induction therapy with a topical steroid can be useful before starting cyclosporine for the long term. Once the patients are in a successful maintenance phase, topical steroids can be used for acute flare-ups triggered by travel, allergies, respiratory infection or exposure to environmental irritants.

3.2.3 Topical Ocular Cyclosporine A

In December 2002, an ophthalmic formulation containing 0.05% cyclosporine A (CyA) was approved by the United States Food and Drug Administration (FDA) to treat dry eye disease at a recommended twice daily dose, based on the results of two randomized control trials in patients with keratoconjunctivitis sicca. In the absence of literature data about topical CyA use in older primary SjS patients, we have extrapolated the results obtained in older populations with dry eye disease (Supplementary Table 1, see electronic supplementary material [ESM]). Significantly more patients preferred the eye treated with topical CyA to the eye treated with artificial tears [52–56]. One study demonstrated that the use of 0.1% CyA cationic emulsion versus vehicle was statistically superior to vehicle in improving both signs and symptoms of dry eye disease in the overall patient population (especially in those with severe keratitis) and in patients with SjS/severe dry eye disease, but there was only a trend towards greater benefits in the overall SjS population with a safety profile consistent with ophthalmic CyA use [55]. The effect of decreasing topical CyA from twice-daily to once-daily administration in patients with dry eye disease demonstrated significant improvement in tear film break-up and lissamine green staining score, but fluorescein staining score, Schirmer test results and Ocular Surface Disease Index did not change significantly, although 14% in the once-daily group ended the study early because of worsening dry eye symptoms ($p < 0.05$) and went back to twice-daily administration [57]. No overall difference in safety or effectiveness has been observed between older and younger patients according to the prescribing information of topical CyA.

3.2.4 Serum Tear Drops

In SjS patients, the role of autologous or allogenic serum has been tested in small uncontrolled studies showing inconsistent benefits (no improvement in all objective ocular outcomes evaluated) with no evidence of an effect after 2 weeks of treatment [58]. There are no specific studies carried out in older populations. The difficulties in preparation, the need to refrigerate the drops, and the potential risk of contamination should be taken into account [50, 59]. The Task Force recommended that serum tear drops may be considered in patients who are non-responders or intolerant to topical CyA tear drops [16].

3.2.5 Plugs

A recent Cochrane systematic review of the literature reviewing the use of plugs for dry eye syndrome [60] found that the evidence was very limited and concluded that improvements in subjective and objective ocular outcomes

were inconclusive [16]. Only one study was carried out in older primary SjS patients showing a significant improvement with respect to baseline scores in three out of five ocular outcomes [61]. One prospective (mean age 65 years) and one randomized control trial (mean age around 65 years) evaluated punctal plug use in older people and demonstrated increased aqueous tear volume and a greater improvement in strip meniscometry, rose bengal and fluorescein staining scores [62, 63]. The most common adverse events induced by the use of plugs are epiphora (6–9%) and plug displacement (3–8.5%) [64, 65], while ocular irritation, ocular pain and headache were rarely described [64] (Supplementary Table 2, see ESM).

4 Management of Non-Specific General Symptoms

Patients with primary SjS often present with general symptoms, the most frequent of which are non-inflammatory joint/muscle pain and fatigue/weakness, which may have a much greater impact on health-related quality of life than sicca features, as reported in cross-sectional studies [66–68]. Unfortunately, these symptoms are very non-specific and could be related to a wide range of concomitant pathologies, most of which are especially prevalent in older people (osteoarthritis, hypothyroidism, hypocortisolism, vitamin deficiencies, depression, neoplasia). A specific comment is needed on the association between SjS and some somatic functional syndromes such as chronic fatigue syndrome and fibromyalgia, whose peak of incidence occurs in the same population subset as SjS (middle-aged women) [69], and a higher level of fatigue was related to higher level of depressive symptoms, especially in older women [70].

It is estimated that 45–80% of older people report some kind of pain. Pain lasting three or more months affects 62% of people aged > 75 years, with the most common type being musculoskeletal pain [71, 72]. Chronic pain due to musculoskeletal conditions can have a tremendous negative impact on the everyday life of older individuals [72]. To live with chronic pain as an older adult is also associated with a substantially greater risk of developing disability and mobility limitations over time [73]. The phenotypic expression of chronic pain in older adults can be influenced by co-morbid diseases (e.g. diabetes, cancer, depression, Alzheimer's disease, etc.), changes in physiological competency (e.g. drug metabolism/elimination) or cognitive reserve. More than 20% of the older population take some form of analgesic for > 6 months (i.e. they have chronic pain) [73].

With respect to the therapeutic management of SjS-related musculoskeletal pain, a differentiation must be made clinically between joint pain (arthralgia) and joint inflammation (arthritis, tenosynovitis). In patients presenting

with acute musculoskeletal pain, consider acetaminophen or NSAIDs for symptomatic relief, always for less than 7–10 consecutive days at full dosage and considering the side effects and underlying comorbid diseases. Off-label use of biological agents to treat only musculoskeletal pain (even as rescue therapy) is not currently warranted. In patients with chronic, daily non-inflammatory pain, the management must be completely different, avoiding the repeated use of NSAIDs or glucocorticoids [16].

Compared with younger adults, safe and effective treatment of pain in older adults requires specialized knowledge and training in pain management. Treatment plans require knowledge of concurrent medications and the potential impact and influence of comorbid medical and psychosocial problems. Important drug interactions that can affect analgesic actions and that can yield side effects are crucial to understanding this population because it has a much-reduced physiologic reserve than a younger adult population [73].

Non-pharmacological management of pain should be emphasized, instead of going straight to prescribing medications for the symptoms. Therefore, the first therapeutic step should be to follow the same recommendations as those proposed for general chronic pain, by suggesting that physical activity and aerobic exercise are interventions with few adverse events that may reduce pain severity and improve physical function [16, 74]. Exercise and physical activity comprise the core strategies, which the American Geriatric Society has identified in their recommendations in the care for older adults with chronic pain [75–77]. The intervention, based on a practical physical exercise programme in persons with musculoskeletal pain, had a positive effect on pain-related disability, pain severity, level of physical activity, health-related quality of life, management of everyday life, and self-efficacy [78–82].

Because older patients are among the highest users of analgesics, the efficacy and safety of their use in this subpopulation is a relevant point. Paracetamol and NSAIDs are the most frequently used pain medications [83], while pregabalin, gabapentin, amitriptyline and duloxetine are among those that cause adverse effects, often requiring stopping the medication [84]. Safety concerns associated with the use of paracetamol, aspirin or ibuprofen include gastrointestinal adverse events and concomitant use of prohibited medication with an odds ratio (OR) that increased with the number of medications used, from 1.54 to 1.87 for one medication to 2.35–2.72 for three or more medications [85]. Gastrointestinal complications were the most frequent adverse event encountered in the different types of NSAIDs, with the drug needing to be withdrawn in some cases because of them [85]. Despite the lack of available evidence in primary SjS patients, experts believe that topical formulations of NSAIDs may be effective for local pain with fewer side effects in comparison with oral administration [16, 86, 87].

Some studies in older patients have reported the efficacy of fentanyl 1-day patch but with a high incidence of adverse events in comparison with the control group [88], and better improvement in musculoskeletal pain with buprenorphine patches plus oral paracetamol than with that obtained with an oral codeine/paracetamol combination tablet in older adults with osteoarthritis [89]. Patients receiving seven patches plus oral paracetamol needed significantly less escape medication (ibuprofen) than those receiving co-codamol tablets. The incidence of adverse events was comparable between the groups and withdrawal rates were high in both groups [89].

5 Management of Systemic Sjögren's Syndrome

The management of systemic features of primary SjS must be tailored to the specific organ involved and the severity evaluated by the EULAR Sjögren's syndrome disease activity index (ESSDAI) [90]. As an overall rule, systemic therapies may be considered for most patients presenting with at least moderate activity in one clinical domain, or with a global moderate disease activity score (score ≥ 5) [16]. With respect to the diagnosis of the disease at older ages, the largest reported cohort found some significant differences in patients with an older diagnosis (> 70 years) who showed a higher frequency of positive oral tests and a lower frequency of anti-Ro/La autoantibodies and low complement 3 levels [91]. In the same cohort, we also found that patients with an older onset (> 65 years) showed a lower mean ESSDAI, a lower mean ClinESSDAI and low disease activity states in comparison with younger ages [92]. However, the most striking differences were reported for organ-by-organ systemic activity, since an older onset was associated with an enhanced risk for presenting activity at articular, pulmonary, muscular and peripheral nervous system domains [91, 93].

5.1 Glucocorticoids

The EULAR Task Force recommended that glucocorticoids should be used at the minimum dose and length of time necessary to control active systemic SjS. However, the frequent use of glucocorticoids in clinical practice in primary SjS patients [90, 94, 95] is not supported by reliable scientific evidence since no controlled study has specifically evaluated their use for systemic disease. The EULAR guidelines recommend the use of pulses of methylprednisolone followed by doses of ≤ 0.5 mg/kg/day as induction therapy in severe presentations, and doses < 0.5 mg/kg/day in moderate/less-severe presentations, with a final target of withdrawing glucocorticoids in inactive patients as soon as possible or at least trying to target a maintenance dose of ≤ 5 mg daily

with the aid of glucocorticoid-sparing immunosuppressive agents. No available data in primary SjS patients support specific recommendations on the rate of de-escalation of the glucocorticoid dose, or when a glucocorticoid-sparing agent should be added, or the length of glucocorticoid therapy, although the EULAR Task Force recommend tapering glucocorticoids as rapidly as clinically feasible [16].

Adverse events are frequent in patients treated with long-term glucocorticoids, including hyperglycaemia, cataracts, gastropathies, *facies lunaris* and candidiasis, and showed a homogeneous incidence, independent of the patient's age [96, 97]. Older patients are more exposed to the side effects of glucocorticoids [98], mainly collapses of vertebral bodies [99], and several studies in older patients with other autoimmune diseases have reported an enhanced risk for developing several adverse events. In patients with anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV) aged 65 years or older, initial high-dose glucocorticoid administration was an independent predictor of early severe infection, and patients with early severe infections had a high mortality rate [100]. Another relevant finding is that systemic glucocorticoids increased venous thromboembolism risk in patients (aged > 70 years) among present (adjusted incidence rate ratio [IRR] 2.31), new (IRR 3.06), continuing (IRR 2.02) or recent (IRR 1.18) users, but not among former users (IRR 0.94) [101]. In older inflammatory bowel disease patients, a prolonged corticosteroid exposure was associated with severe adverse events, and dose-related adverse events appeared in 40% of older patients exposed to corticosteroids for longer, osteoporosis in 16% and fractures related to osteoporosis and osteonecrosis in 15%. The considerable prevalence of calcium and vitamin D deficiency and malabsorption in older patients stresses the importance of early and regular bone densitometry assessments [102]. Other adverse events of glucocorticoids, which are more pronounced among older patients, include altered mental state and depression; retention of fluids, which is particularly significant in patients with underlying hypertension; congestive heart failure; diabetes and renal disease; and glaucoma induced by corticosteroids [102] (Supplementary Table 3, see ESM).

5.2 Synthetic Immunosuppressive Agents

According to the EULAR recommendations, synthetic immunosuppressive agents should mainly be used as glucocorticoid-sparing agents, with no evidence supporting the choice of one agent over another. Based on the potential development of chronic damage in patients with uncontrolled systemic disease, some patients may require long-term therapy with glucocorticoids, especially those with severe organ impairments [90, 94, 95]. In these patients, the addition of immunosuppressive agents such as glucocorticoid-sparing

agents is justified, always weighing the potential benefits and risks, although the use of immunosuppressive agents in primary SjS has the same limited level of evidence as reported for the use of glucocorticoids [16].

The available data, although limited, suggest that disease-modifying antirheumatic drugs (DMARDs), including some biological agents, have a similar effect on old and young patients, while maintaining excellent adverse effect profiles; older patients should not, therefore, be excluded from the optimal treatment provided by these medications. Clinicians must concurrently take into consideration the potential increase in the risk of drug toxicities, recognizing the need to adjust the therapy to match the characteristics of individual patients (i.e. co-morbidities, renal function, concomitant use of medication or polypharmacy), and prescribe the lowest possible effective dosage. Reduction in renal function in older subjects, particularly glomerular filtration rate, affects the clearance of many drugs. The clinical importance of such reductions of renal excretion is dependent on the likely toxicity of the drug. Drugs with a narrow therapeutic index (like some DMARDs) have serious adverse effects if they accumulate only marginally more than intended. Considering the lack of studies analysing the efficacy and safety profile of immunosuppressive agents in older primary SjS patients, we have evaluated some studies carried out in older patients with other systemic autoimmune diseases (Supplementary Table 4, see ESM).

Idiosyncratic reactions that develop in approximately 5% of patients are among the adverse events associated with azathioprine, including fever, pancreatitis and hepatitis; leucopenia may also occur at any time during the therapy and is largely determined by the enzymatic activity of thiopurine methyltransferase. Another risk that increases is that of leucopenia when azathioprine is prescribed with clotrimazole or angiotensin-converting enzyme inhibitors; similarly, bone marrow toxicity may occur when azathioprine is used with allopurinol and the dose is reduced to one quarter of the standard dose [102]. Azathioprine has been successfully used in the treatment of older patients with autoimmune hepatitis, and although patients aged > 60 years failed glucocorticoid treatment less commonly than those aged < 30 years [103], they are more likely to discontinue azathioprine secondary to intolerance as opposed to lack of efficacy [104]. Adverse effects of azathioprine included gastrointestinal intolerance, including nausea, vomiting, abdominal pain, cholestasis [104]; elevation of hepatic enzymes [105]; and opportunistic infections, including tuberculosis and herpes zoster [104]. The development of severe adverse events during the follow-up was seen during the first year of treatment and azathioprine was associated with the discontinuation of treatment because of adverse events in 46% of patients [105]. In patients with bullous pemphigoid, mycophenolate mofetil [MMF] and azathioprine have demonstrated similar efficacy

although MMF showed a significantly lower liver toxicity profile than azathioprine [106]. In older patients with microscopic polyangiitis with mild to moderate renal involvement treated with MMF, adverse events were mild, transient, and responsive to dose adjustments in all patients except one [107]. As a result, most of the studies performed so far have not revealed geriatric-specific problems that might limit the usefulness of MMF in older patients. Older populations are nevertheless more likely to have age-related kidney, liver or heart failure, and this may require physicians to proceed with caution and to adjust the dose of MMF patients receive.

As regards methotrexate, physicians should be cautious in selecting the dose for an older patient considering the higher frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other pharmacological therapy (i.e. one that might interfere with renal function, such as methotrexate or folate metabolism) in this group of patients. As a decline in renal function may be associated with higher levels of adverse events and serum creatinine, measurements may overestimate renal function in older patients. More accurate methods (creatinine clearance, for example) should be taken into consideration. It is important to monitor older patients closely for early signs of hepatic, renal and bone marrow toxicity. In situations where use is long term, it may be possible to reduce certain toxicities by supplementing folates. Post-marketing experience indicates that bone marrow suppression, thrombocytopenia and pneumonitis may increase with age.

5.3 Biological Agents

The emergence of biological therapies in this century has increased the therapeutic armamentarium available for treating severe primary SjS, although their use in clinical practice is clearly limited by the lack of licensing. B cell targeted therapies are the most frequently tested biological drugs, and the most widely studied B-cell target therapy is rituximab [108–120]. However, increased age remains a significant barrier to a successful treat-to-target biological approach in elderly patients with autoimmune diseases, and physicians often prefer less aggressive treatment for older patients [121]. Similarly, the use of multiple conventional synthetic DMARDs or biological DMARDs in older patients with rheumatoid arthritis (RA) is markedly lower compared with young patients, where the decision was not related to the disease activity, the disease duration or the presence of comorbidities [122–125]. There are no studies specifically addressing biological treatment in older patients with primary SjS. The evidence was extrapolated from studies evaluating elderly populations with other autoimmune diseases. Rituximab has showed efficacy in elderly patients with cryoglobulinaemic and anti-neutrophilic cytoplasmic autoantibodies (ANCA) vasculitis, and in those with RA,

with no new safety concerns [126, 127]. One study has compared the safety of rituximab biosimilar with reference rituximab in patients ≥ 65 years with RA, and no safety risks were detected when patients switched from reference rituximab to the biosimilar [128].

The EULAR Task Force recommended that the systemic organ-specific therapeutic approach may, as a general rule, follow the sequential (or combined) use of glucocorticoids, immunosuppressive agents and biologics. This sequential use of the three main categories of immunosuppressive agents in primary SjS was based on a similar approach to that reported for other systemic autoimmune diseases such as SLE or vasculitis, with no controlled studies supporting this approach in primary SjS. As a general rule, for most systemic involvement, glucocorticoids may be considered the first-line option in patients with active systemic disease, and immunosuppressive agents and biologics as second-/third-line options to be used in patients intolerant or refractory to glucocorticoids, those with severe disease or those in whom long-term glucocorticoid use is anticipated. However, considering the deleterious effects of the use of glucocorticoids in older populations and the enhanced risk of adverse events for synthetic immunosuppressive agents, the use of rituximab could be considered as first- or second-line therapy, especially in older patients with the two more severe systemic complications of the disease (cryoglobulinaemic vasculitis and lymphoma), always with a careful case-by-case assessment of the use of rituximab in an off-label context, evaluating potential benefits and adverse events patient by patient and taking into account the fact that their use will depend on drug availability and national regulations [16]. With respect to lymphoma, the EULAR Task Force recommended that treatment should be individualized according to the specific histological subtype and disease stage. In order to better tailor the best therapeutic strategy for older primary SjS patients affected by lymphoma, a careful assessment of performance status, comorbidities and age should be done, above all in older patients. The choice of the best front-line treatment for patients affected by diffuse large B-cell lymphoma (DLBCL) should be made on the basis of age, performance status, stage and prognostic score [129]. In older patients with DLBCL, the addition of rituximab to standard cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy significantly reduced the risk of treatment failure and death without relevant toxicity [130]. Nowadays, bendamustine is used in combination with rituximab and has been shown to be both efficient and well tolerated in indolent non-Hodgkin's lymphomas, and is used as first-line treatment in older patients [131]. The safety profile of bendamustine and rituximab revealed that the most frequent grade 3–4 adverse event was neutropenia (37.8%) [131]. When considering the use of cyclophosphamide in older patients, the dose adjustment should be done

according to serum albumin levels and the patient's body weight and gender [132]. Another prospective trial strongly suggested that additive radiotherapy [133] to bulky sites abrogates bulky disease as a risk factor and improves outcome of older patients with aggressive B-cell lymphoma [134] (Supplementary Table 5, see ESM).

6 Conclusions

SjS is a systemic autoimmune disease usually diagnosed in middle-aged people, although in 20% of patients the diagnosis can be established after the age of 65 years. The recent publication of the EULAR therapeutic guidelines for the treatment of primary SjS has been an important step forward after reaching the consensus of more than 100 specialists in the disease, with the proposal of a set of recommendations that can be applied to any patient with SjS regardless of their age. However, the therapeutic management of the disease in older patients has some differential nuances, although unfortunately the scientific evidence available in this regard is practically nil, and many of the aspects we propose have been extrapolated from studies carried out in similar diseases.

In this systematic review, we have evaluated the EULAR recommendations through the prism of their application to older patients. First of all, it is important to know that the ageing process affects the function of the exocrine glands, and therefore, measurement of glandular function is worthwhile in older patients (e.g. salivary flows are lower in older people). Treatment of the effects of glandular dysfunction can be tailored to the actual residual secretory potential of these glands, including advice on which agents might be effective to relieve the sicca complaints in a particular patient as well as which preventive regimen should be prescribed to reduce the risk of developing dental caries. In addition, certain conditions that are common in older adults such as diabetes mellitus or frequent polypharmacy can also contribute to glandular dysfunction, causing a higher frequency (and worsening) of oral and ocular dryness. The frequent comorbidities in older people, together with the chronic use of medications, may also force us to modify the use of many of the drugs included in the guidelines, also with regard to their often negative effect on glandular function. Age-related changes in drug metabolism and elimination are important to consider when prescribing muscarinic agonists to patients aged > 65 years, mainly because older patients are more likely to have pulmonary, liver, kidney or heart-related comorbidities, which may require caution when these drugs are used.

It is also important to monitor the use of eye drops containing corticoids due to the increased risk of developing cataracts, a frequent ocular complication in the older

population. The use of systemic corticosteroids should be limited as much as possible due to their potential risk of causing osteoporosis, metabolic alterations and infections, and in case of severe systemic SjS-related manifestations, it is always preferable to use the lowest daily dose and for the shortest time possible with the use of corticosteroid-sparing agents like immunosuppressants. In contrast, the majority of drugs that can be used topically (pilocarpine rinses, eye drops containing topical NSAIDs or CyA, topical dermal formulations of NSAIDs) have shown an acceptable safety profile in older patients. Likewise, rituximab has been widely used in older people with other pathologies (vasculitis, lymphoma) without being associated with a greater number of adverse events.

The personalized treatment of primary SjS, one of the key principles under which the optimal management of the disease is supported, is even more important in older patients. The comprehensive evaluation of the medical history of each patient is essential when most of the drugs included in the EULAR guidelines are prescribed in older people, with special attention to factors frequently related to ageing, such as polypharmacy, the existence of cardiovascular, metabolic, pulmonary or renal comorbidities, or the enhanced susceptibility to infection.

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Declarations

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Ethics Approval Not applicable to a review.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data All data were sourced from academic journals, are listed in the references, and are available to the public.

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References

- Mariette X, Criswell LA. Primary Sjögren's syndrome. *N Engl J Med*. 2018;378:931–9.
- Brito-Zerón P, Baldini C, Bootsma H, et al. Sjögren syndrome. *Nat Rev Dis Primers*. 2016;2:16047.
- Kvarnstrom M, Ottosson V, Nordmark B, et al. Incident cases of primary Sjögren's syndrome during a 5-year period in Stockholm County: a descriptive study of the patients and their characteristics. *Scand J Rheumatol*. 2015;44:135–42.
- Weng MY, Huang YT, Liu MF, et al. Incidence and mortality of treated primary Sjögren's syndrome in Taiwan: a population-based study. *J Rheumatol*. 2011;38:706–8.
- Kabasakal Y, Kitapcioglu G, Turk T, et al. The prevalence of Sjögren's syndrome in adult women. *Scand J Rheumatol*. 2006;35:379–83.
- Maldini C, Seror R, Fain O, et al. Epidemiology of primary Sjögren's syndrome in a French multiracial/multiethnic area. *Arthritis Care Res (Hoboken)*. 2014;66:454–63.
- Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, et al. Primary Sjögren syndrome. *BMJ*. 2012;344:e3821.
- Moerman RV, Bootsma H, Kroese FGM, et al. Sjögren's syndrome in older patients: aetiology, diagnosis and management. *Drugs Aging*. 2013;30:137–53.
- Wolff A, Joshi RK, Ekström J, et al. A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: a systematic review sponsored by the world workshop on oral medicine VI. *Drugs R D*. 2017;17:1–28.
- Vissink A, Spijkervet FK, Van Nieuw Amerongen A. Aging and saliva: a review of the literature. *Spec Care Dent*. 1996;16:95–103.
- Ship JA, Pillemer SR, Baum BJ. Xerostomia and the geriatric patient. *J Am Geriatr Soc*. 2002;50:535–43.
- Astor FC, Hanft KL, Ciocon JO. Xerostomia: a prevalent condition in the elderly. *Ear Nose Throat J*. 1999;78:476–9.
- Marchini L, Ettinger R, Hartshorn J. Personalized dental caries management for frail older adults and persons with special needs. *Dent Clin North Am*. 2019;63:631–51.
- Tishler M, Yaron I, Shirazi I, et al. Clinical and immunological characteristics of elderly onset Sjögren's syndrome: a comparison with younger onset disease. *J Rheumatol*. 2001;28:795–7.
- Brito-Zerón P, Acar-Denizli N, Ng WF, et al. Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjögren's syndrome. *Rheumatology (Oxford)*. 2020;59:2350–9.
- Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al; EULAR-Sjögren Syndrome Task Force Group. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis*. 2020;79:3–18.
- Varoni EM, Federighi V, Decani S, et al. The effect of clinical setting on the unstimulated salivary flow rate. *Arch Oral Biol*. 2016;69:7–12.
- Oncul B, Karakis D, Dogruman F. The effect of two artificial salivas on the adhesion of *Candida albicans* to heat polymerized acrylic resin. *J Adv Prosthodont*. 2015;7:93–7.
- Gómez-Moreno G, Cabrera-Ayala M, Aguilar-Salvatierra A, et al. Evaluation of the efficacy of a topical sialogogue spray containing malic acid 1% in elderly people with xerostomia: a double-blind, randomized clinical trial. *Gerodontology*. 2014;31:274–80.
- Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. *J Am Dentrit Assoc*. 1987;115:581–584.
- Thomson WM, Chalmers JM, Spencer AJ, et al. The Xerostomia inventory: a multi-item approach to measuring dry mouth. *Community Dent Health*. 1999;16:12–7.
- Choromańska M, Klimiuk A, Kostecka-Sochoń P, et al. Anti-oxidant defence, oxidative stress and oxidative damage in saliva, plasma and erythrocytes of dementia patients. Can salivary AGE be a marker of dementia? *Int J Mol Sci*. 2017;18:2205.
- Fischer D, Ship JA. Effect of age on variability of parotid salivary gland flow rates over time. *Age Ageing*. 1999;28:557–61.
- Närhi TO, Meurman JH, Ainamo A, et al. Association between salivary flow rate and the use of systemic medication among 76-, 81-, and 86-year-old inhabitants in Helsinki, Finland. *J Dent Res*. 1992;71:1875–80.
- Smith CH, Boland B, Daureeawoo Y, et al. Effect of aging on stimulated salivary flow in adults. *J Am Geriatr Soc*. 2013;61:805–8.
- Affoo RH, Foley N, Garrick R, et al. Meta-analysis of salivary flow rates in young and older adults. *J Am Geriatr Soc*. 2015;63:2142–51.
- Kagami H, Hayashi T, Shigetomi T, et al. Assessment of the effects of aging and medication on salivary gland function in patients with xerostomia using 99mTc-scintigraphy. *Clin Trial Nagoya J Med Sci*. 1995;58:149–55.
- Iwasaki M, Borgnakke WS, Yoshihara A, et al. Hyposalivation and 10-year all-cause mortality in an elderly Japanese population. *Gerodontology*. 2018;35:87–94.
- Handelman SL, Baric JM, Saunders RH, et al. Hyposalivatory drug use, whole stimulated salivary flow, and mouth dryness in older, long-term care residents. *Spec Care Dentist*. 1989;9:12–8.
- Chávez EM, Borrell LN, Taylor GW, et al. A longitudinal analysis of salivary flow in control subjects and older adults with type 2 diabetes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;91:166–73.
- Närhi TO, Vehkalahti MM, Siukosaari P, et al. Salivary findings, daily medication and root caries in the old elderly. *Caries Res*. 1998;32:5–9.
- Gonsalves WC, Wrightson AS, Henry RG. Common oral conditions in older persons. *Am Fam Physician*. 2008;78:845–52.
- Vissink A, De Jong HP, Busscher HJ, et al. Wetting properties of human saliva and saliva substitutes. *J Dent Res*. 1986;65:1121–4.
- Bardellini E, Amadori F, Conti G, et al. Effectiveness of a spray containing 1% malic acid in patients with xerostomia induced by graft-versus-host disease. *Med Oral Patol Oral Cir Bucal*. 2019;24:e190–4.
- Pilocarpine nitrate ≥ 98.5% extra pure. Safety data sheet according to Regulation (EC) No. 1907/2006 (REACH), amended by 2015/830/EU. Article number: 7523. Date of compilation: 2019-10-2. <https://www.carlroth.com/medias/SDB-7523-GB-EN.pdf?>
- Davies AN, Daniels C, Pugh R, et al. A comparison of artificial saliva and pilocarpine in the management of xerostomia in patients with advanced cancer. *Palliat Med*. 1998;12:105–11.
- Tanigawa T, Yamashita J, Sato T, et al. Efficacy and safety of pilocarpine mouthwash in elderly patients with xerostomia. *Spec Care Dent*. 2015;35:164–9.
- Olsson H, Axéll T. Objective and subjective efficacy of saliva substitutes containing mucin and carboxymethylcellulose. *Scand J Dent Res*. 1991;99:316–9.
- Matear DW, Barbaro J. Effectiveness of saliva substitute products in the treatment of dry mouth in the elderly: a pilot study. *J R Soc Promot Health*. 2005;125:35–41.
- Dalodom S, Lam-Ubol A, Jeanmaneechotechai S, et al. Influence of oral moisturizing jelly as a saliva substitute for the relief of xerostomia in elderly patients with hypertension and diabetes mellitus. *Geriatr Nurs*. 2016;37:101–9.
- Vinke J, Kaper HJ, Vissink A, et al. Dry mouth: saliva substitutes which adsorb and modify existing salivary condition films improve oral lubrication. *Clin Oral Investig*. 2020. <https://doi.org/10.1007/s00784-020-03272-x>.

42. Su N, Marek CL, Ching V, et al. Caries prevention for patients with dry mouth. *J Can Dent Assoc.* 2011;77:b85.
43. Weyant RJ, Tracy SL, Anselmo TT, et al. Topical fluoride for caries prevention: executive summary of the updated clinical recommendations and supporting systematic review. *J Am Dent Assoc.* 2013;144:1279–91.
44. Asrini Noor N, Rahayu T, Gondhowiardjo TD. Prevalence of dry eye and its subtypes in an elderly population with cataracts in Indonesia. *Clin Ophthalmol.* 2020;14:2143–50.
45. Fernandez CA, Galor A, Arheart KL, et al. Dry eye syndrome, posttraumatic stress disorder, and depression in an older male veteran population. *Invest Ophthalmol Vis Sci.* 2013;54:3666–72.
46. Kaiserman I, Kaiserman N, Nakar S, et al. Dry eye in diabetic patients. *Am J Ophthalmol.* 2005;139:498–503.
47. Wegener AR, Meyer LM, Schönfeld CL. Effect of viscous agents on corneal density in dry eye disease. *J Ocul Pharmacol Ther.* 2015;31:504–8.
48. Vandermeer G, Chamy Y, Pisella PJ. Comparison of objective optical quality measured by double-pass aberrometry in patients with moderate dry eye: normal saline vs. artificial tears: A pilot study. *J Fr Ophthalmol.* 2018;41:238–245.
49. Sharma A, Hindman HB. Aging: a predisposition to dry eyes. *J Ophthalmol.* 2014;2014:781683.
50. Foulks GN, Forstot SL, Donshik PC, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. *Ocul Surf Ocul Surf.* 2015;13:118–32.
51. Avisar R, Robinson A, Appel I, et al. Diclofenac sodium, 0.1% (Voltaren Ophtha), versus sodium chloride, 5%, in the treatment of filamentary keratitis. *Cornea.* 2000;19:145–7.
52. Perry HD, Solomon R, Donnenfeld ED, et al. Evaluation of topical cyclosporine for the treatment of dry eye disease. *Arch Ophthalmol.* 2008;126:1046–50.
53. Wirta D, Torkildsen GL, Moreira HR, et al. A clinical phase II study to assess efficacy, safety, and tolerability of waterfree cyclosporine formulation for treatment of dry eye disease. *Ophthalmology.* 2019;126:792–800.
54. Donnenfeld ED, Solomon R, Roberts CW, et al. Cyclosporine 0.05% to improve visual outcomes after multifocal intraocular lens implantation. *J Cataract Refract Surg.* 2010;36:1095–100.
55. Chung YW, Oh TH, Chung SK. The effect of topical cyclosporine 0.05% on dry eye after cataract surgery. *Korean J Ophthalmol.* 2013;27:167–71.
56. Leonardi A, Messmer EM, Labetoulle M, et al. Efficacy and safety of 0.1% ciclosporin A cationic emulsion in dry eye disease: a pooled analysis of two double-masked, randomised, vehicle-controlled phase III clinical studies. *Br J Ophthalmol.* 2019;103:125–131.
57. Su MY, Perry HD, Barsam A, et al. The effect of decreasing the dosage of cyclosporine A 0.05% on dry eye disease after 1 year of twice-daily therapy. *Cornea.* 2011; 30:1098–104.
58. Pan Q, Angelina A, Marrone M, et al. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev.* 2017;252.
59. Rauz S, Koay S-Y, Foot B, et al. The Royal College of ophthalmologists guidelines on serum eye drops for the treatment of severe ocular surface disease: full report. *Eye (Lond).* 2017. <https://doi.org/10.1038/eye.2017.209>.
60. Ervin A-M, Law A, Pucker AD, et al. Punctal occlusion for dry eye syndrome. *Cochrane Database Syst Rev.* 2017;140.
61. Qiu W, Liu Z, Ao M, et al. Punctal plugs versus artificial tears for treating primary Sjögren's syndrome with keratoconjunctivitis sicca: a comparative observation of their effects on visual function. *Rheumatol Int.* 2013;33:2543–8.
62. Ibrahim OMA, Dogru M, Kojima T, et al. OCT assessment of tear meniscus after punctal occlusion in dry eye disease. *Optom Vis Sci.* 2012;89:E770–6.
63. Altan-Yaycioglu R, Gencoglu EA, Akova YA, et al. Silicone versus collagen plugs for treating dry eye: results of a prospective randomized trial including lacrimal scintigraphy. *Am J Ophthalmol.* 2005;140:88–93.
64. Jones CE, Anklesaria M, Alan D Gordon AD, et al. Retrospective safety study of the herrick lacrimal plug: a device used to occlude the lacrimal canaliculus. *CLAO J.* 2002;28:206–10.
65. Sherwin JC, Ratnarajan G, Elahi B, et al. Effect of a punctal plug on ocular surface disease in patients using topical prostaglandin analogues: a randomized controlled trial. *Clin Exp Ophthalmol.* 2018;46:888–94.
66. Cornec D, Devauchelle-Pensec V, Mariette X, et al. Severe Health-Related quality of life impairment in active primary Sjögren's syndrome and Patient-Reported outcomes: data from a large therapeutic trial. *Arthritis Care Res.* 2017;69:528–35.
67. Koh JH, Kwok SK, Lee J, et al. Pain, xerostomia, and younger age are major determinants of fatigue in Korean patients with primary Sjögren's syndrome: a cohort study. *Scand J Rheumatol.* 2017;46:49–55.
68. Milin M, Cornec D, Chastaing M, et al. Sicca symptoms are associated with similar fatigue, anxiety, depression, and quality-of-life impairments in patients with and without primary Sjögren's syndrome. *Joint Bone Spine.* 2016;83:681–5.
69. Brito-Zerón P, Retamozo S, Ramos-Casals M. Phenotyping Sjögren's syndrome: towards a personalised management of the disease. *Clin Exp Rheumatol.* 2018;36(Suppl 112):198–209.
70. Mänty M, Rantanen T, Era P, et al. Fatigue and depressive symptoms in older people. *J Appl Gerontol.* 2014;33:505–14.
71. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380:2163–96.
72. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education Washington (DC): National Academies Press (US); 2011. The National Academies Collection: Reports funded by National Institutes of Health.
73. Arneric SP, Laird JMA, Chappell AS, et al. Tailoring chronic pain treatments for the elderly: are we prepared for the challenge? *Drug Discov Today.* 2014;19:8–17.
74. Geneen LJ, Moore RA, Clarke C, et al. Physical activity and exercise for chronic pain in adults: an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2017;4.
75. Andrew R, Derry S, Taylor RS, et al. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Pract.* 2014;14:79–94.
76. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. *BMJ.* 2015;350:h532.
77. AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. *J Am Geriatr Soc.* 2002;50:S205–24.
78. Ferrell BA, Josephson KR, Pollan AM, et al. A randomized trial of walking versus physical methods for chronic pain management. *Aging (Milano).* 1997;9:99–105.
79. Lihavainen K, Sipilä S, Rantanen T, et al. Effects of comprehensive geriatric assessment and targeted intervention on mobility in persons aged 75 years and over: a randomized controlled trial. *Clin Rehabil.* 2012;26:314–26.
80. Cederbom S, Leveille SG, Bergland A. Effects of a behavioral medicine intervention on pain, health, and behavior among community-dwelling older adults: a randomized controlled trial. *Clin Interv Aging.* 2019;14:1207–20.
81. Quehenberger V, Cichocki M, Krajic K. Sustainable effects of a low-threshold physical activity intervention on health-related

- quality of life in residential aged care. *Clin Interv Aging*. 2014;9:1853–64.
82. Hirase T, Kataoka H, Nakano J, et al. Effects of a psychosocial intervention programme combined with exercise in community-dwelling older adults with chronic pain: a randomized controlled trial. *Eur J Pain*. 2018;22:592–600.
 83. Rapo-Pylkkö S, Haanpää M, Liira H. Chronic pain among community-dwelling elderly: a population-based clinical study. *Scand J Prim Health Care*. 2016;34:159–64.
 84. Kennedy MC, Cousins G, Henman MC. Analgesic use by ageing and elderly patients with chronic non-malignant pain: a qualitative study. *Int J Clin Pharm*. 2017;39:798–807.
 85. Moore N, Charlesworth A, Van Ganse E, et al. Risk factors for adverse events in analgesic drug users: results from the PAIN study. *Pharmacoepidemiol Drug Saf*. 2003;12:601–10.
 86. Loveless MS, Fry AL. Pharmacologic therapies in musculoskeletal conditions. *Med Clin North Am*. 2016;100:869–90.
 87. Derry S, Conaghan P, Da Silva JAP, et al. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane database Syst Rev*. 2016;36.
 88. Arai T, Kashimoto Y, Ukyo Y, et al. Two placebo-controlled, randomized withdrawal studies to evaluate the fentanyl 1-day patch in opioid-naïve patients with chronic pain. *Curr Med Res Opin*. 2015;31:2207–18.
 89. Conaghan PG, O'Brien CM, Wilson M, et al. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomised trial. *Osteoarthritis Cartil*. 2011;19:930–8.
 90. Flores-Chávez A, Kostov B, Solans R, et al. Severe, life-threatening phenotype of primary Sjögren's syndrome: clinical characterisation and outcomes in 1580 patients (GEAS-SS registry). *Clin Exp Rheumatol*. 2018;36(Suppl 112):121–9.
 91. Brito-Zerón P, Acar-Denizli N, Ng WF, et al. How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). Comparative Study. *Clin Exp Rheumatol*. 2018;36(Suppl 112):102–12.
 92. Brito-Zerón P, Acar-Denizli N, Ng WF, et al; Sjögren Big Data Consortium. Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjögren's syndrome. *Rheumatology (Oxford)*. 2020;59:2350–2359.
 93. Brito-Zerón P, Kostov B, Solans R, et al. Systemic activity and mortality in primary Sjögren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. *Ann Rheum Dis*. 2016;75:348–55.
 94. Gheitasi H, Kostov B, Solans R, et al. How are we treating our systemic patients with primary Sjögren syndrome? analysis of 1120 patients. *Int Immunopharmacol*. 2015;27:194–9.
 95. Sandhya P, Jeyaseelan L, Scofield RH, et al. Clinical characteristics and outcome of primary Sjögren's syndrome: a large Asian Indian cohort. *Open Rheumatol J*. 2015;9:36–45.
 96. Splendiani G, Costanzi S, Sturniolo A, et al. Treatment of idiopathic glomerulonephritis in the elderly. Personal data. *Contrib Nephrol*. 1993;105:139–43.
 97. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1999;340:1941–7.
 98. Passerini P, Como G, Viganò E, et al. Idiopathic membranous nephropathy in the elderly. *Nephrol Dial Transpl*. 1993;8:1321–5.
 99. Chevalet P, Barrier JH, Glémarec J, et al. Horton's disease in elderly patients aged over 75: clinical course, complications of corticotherapy. Comparative study of 164 patients. Towards a reduced initial dose. *Rev Med Interne*. 2001;22:624–30.
 100. Waki D, Nishimura K, Tokumasu H, et al. Initial high-dose corticosteroids and renal impairment are risk factors for early severe infections in elderly patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a retrospective observational study. *Medicine (Baltimore)*. 2020;99:e19173.
 101. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA Intern Med*. 2013;173:743–52.
 102. Nimmons D, Limdi JK. Elderly patients and inflammatory bowel disease. *World J Gastrointest Pharmacol Ther*. 2016;7:51–65.
 103. Czaja AJ, Carpenter HA. Distinctive clinical phenotype and treatment outcome of type 1 autoimmune hepatitis in the elderly. *Hepatology*. 2006;43:532–8.
 104. Schramm C, Kanzler S, Büschenfelde KH, et al. Autoimmune hepatitis in the elderly. *Am J Gastroenterol*. 2001;96:1587–91.
 105. Morishita M, Watanabe H, Yan M, et al. Azathioprine intolerance in Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis. *Intern Med*. 2017;56:1645–50.
 106. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol*. 2007;143:1536–42.
 107. Silva F, Specks U, Kalra S, et al. Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement—a prospective, open-label pilot trial. *Clin J Am Soc Nephrol*. 2010;5:445–53.
 108. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. *Ann Intern Med*. 2014;160:233–42.
 109. Bowman SJ, Everett CC, O'Dwyer JL, et al. Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjögren's syndrome. *Arthritis Rheumatol*. 2017;69:1440–50.
 110. Gottenberg J-E. Tolerance and short-term efficacy of rituximab in 43 patients with systemic autoimmune diseases. *Ann Rheum Dis*. 2005;64:913–20.
 111. Mekinian A, Ravaud P, Hatron PY, et al. Efficacy of rituximab in primary Sjögren's syndrome with peripheral nervous system involvement: results from the air registry. *Ann Rheum Dis*. 2012;71:84–7.
 112. Meiners PM, Arends S, Brouwer E, et al. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. *Ann Rheum Dis*. 2012;71:1297–302.
 113. Seror R, Sordet C, Guillemin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. *Ann Rheum Dis*. 2007;66:351–7.
 114. Gottenberg J-E, Cinquetti G, Larroche C, et al. Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the autoimmune and rituximab registry. *Ann Rheum Dis*. 2013;72:1026–31.
 115. Pijpe J, van Imhoff GW, Spijkervet FKL, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. *Arthritis Rheum*. 2005;52:2740–50.
 116. Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). *Arthritis Rheum*. 2007;57:310–7.
 117. St. Clair EW, Levesque MC, Prak ETL, et al. Rituximab therapy for primary Sjögren's syndrome: an open-label clinical trial and mechanistic analysis. *Arthritis Rheum*. 2013;65:1097–106.
 118. Carubbi F, Cipriani P, Marrelli A, et al. Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study. *Arthritis Res Ther*. 2013;15.
 119. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised,

- double-blind, placebo-controlled pilot study. *Ann Rheum Dis.* 2008;67:1541–4.
120. Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2010;62:960–8.
121. Fraenkel L, Rabidou N, Dhar R. Are rheumatologists' treatment decisions influenced by patients' age? *Rheumatology.* 2006;45:1555–7.
122. Tutuncu Z, Reed G, Kremer J, Kavanaugh A. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? *Ann Rheum Dis.* 2006;65:1226–9.
123. Ranganath V, Maranian P, Elashoff D, et al. Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. *Rheumatology (Oxford).* 2013;52:1809–17.
124. Radovits B, Fransen J, Eijssbouts A, et al. Missed opportunities in the treatment of elderly patients with rheumatoid arthritis. *Rheumatology.* 2009;48:906–10.
125. Serhal L, Lwin MN, Holroyd C, et al. Rheumatoid arthritis in the elderly: characteristics and treatment considerations. *Autoimmun Rev.* 2020;19:102528.
126. De Vita S, Quartuccio L, M Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum.* 2012;64:843–53.
127. Charles P, Terrier B, Perrodeau E, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis.* 2018;77:1143–9.
128. Tony HP, Krüger K, Cohen SB, et al. Brief Report: safety and immunogenicity of rituximab biosimilar GP 2013 after switch from reference rituximab in patients with active rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2019;71:88–94.
129. Chiappella A, Martelli M, Angelucci E, et al. Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study. *Lancet Oncol.* 2017;18:1076–88.
130. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346:235–42.
131. Storti S, Spina M, Pesce EA, et al. Rituximab plus bendamustine as front-line treatment in frail elderly (> 70 years) patients with diffuse large B-cell non-Hodgkin lymphoma: a phase II multicenter study of the Fondazione Italiana Linfomi. *Haematologica.* 2018;103:1345–50.
132. Baudry E, Huguet S, Couderc AL, et al. Cyclophosphamide dose adjustment based on body weight and albuminemia in elderly patients treated with R-mini-CHOP. *Cancer Chemother Pharmacol.* 2019;83:775–85.
133. Pollard RP, Pijpe J, Bootsma H, et al. Treatment of mucosa-associated lymphoid tissue lymphoma in Sjögren's syndrome: a retrospective clinical study. *J Rheumatol.* 2011;38:2198–208.
134. Held G, Murawski N, Ziepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol.* 2014;32:1112–8.

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