EULAR tedavi önerileri

Dr Servet Akar

16.10.2022/Aydın

İZMİR KATİP ÇELEBİ ÜNİVERSİTESİ

ROMATOLOJİ

2014

Çıkar ilişkisi

- Konuşmacı, çalışma desteği veya danışmanlık: UCB, Abbvie, Lilly, Novartis, Amgen, Celltrion, Pfizer

EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies

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ABSTRACT

The therapeutic management of Sjögren syndrome (SjS) has not changed substantially in recent decades: treatment decisions remain challenging in clinical practice, without a specific therapeutic target beyond the relief of symptoms as the most important goal. In view of this scenario, the European League Against Rheumatism (EULAR) promoted and supported an international collaborative study (EULAR SS Task Force) aimed at developing the first EULAR evidence and consensus-based recommendations for the management of patients with SjS with topical and systemic medications. The aim was to develop a rational therapeutic approach to SjS patients useful for healthcare professionals, physicians undergoing specialist training, medical students, the pharmaceutical industry and drug regulatory organisations following the 2014 EULAR standardised operating procedures. The Task Force (TF) included specialists in rheumatology, internal medicine, oral health, ophthalmology, gynaecology, dermatology and epidemiology, statisticians, general practitioners, nurses and patient representatives from 30 countries of the 5 continents. Evidence was collected from studies including primary SjS patients fulfilling the 2002/2016 criteria; when no evidence was available, evidence from studies including associated SjS or patients fulfilling previous sets of criteria was considered and extrapolated. The TF endorsed the presentation of general principles for the management of patients with SjS as three overarching, general consensus-based recommendations and 12 specific recommendations that form a logical sequence, starting with the management of the central triplet of symptoms (dryness, fatigue and pain) followed by the management of systemic disease. The recommendations address the use of topical oral (saliva substitutes) and ocular (artificial tear drops, topical non-steroidal anti-inflammatory drugs, topical corticosteroids, topical CyA, serum tear drops) therapies, oral muscarinic agonists (pilocarpine, cevimeline), hydroxychloroquine, oral glucocorticoids, synthetic immunosuppressive agents (cyclophosphamide, azathioprine, methotrexate, leflunomide and mycophenolate), and biological therapies (rituximab, abatacept and belimumab). For each recommendation, levels of evidence (mostly modest) and TF agreement (mostly very high) are provided. The 2019 EULAR recommendations are based on the evidence collected in the last 16 years in the management of primary 2002 SjS patients and on discussions between a large and broadly international TF. The recommendations synthesise current thinking on SjS treatment in a set of overarching principles and recommendations. We hope that the current recommendations will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

INTRODUCTION

Sjögren syndrome (SjS), a systemic autoimmune disease that affects 1–23 persons per 10 000 inhabitants in European countries,[1] presents with a wide spectrum of clinical manifestations and autoantibodies. Antinuclear antibodies are the most frequently detected autoantibodies, anti-Ro/SS-A the most specific, and cryoglobulins and hypocomplementaemia the main prognostic markers.[2] The histological hallmark is a focal infiltration of the exocrine glands by lymphocytes, determined by minor labial salivary gland biopsy. The clinical scenario is dominated by sicca syndrome caused by immune-mediated glandular involvement, accompanied by fatigue, musculoskeletal pain and systemic features in a significant percentage of patients, and complicated by lymphoma in around 2%–5% of patients.[3] When SjS appears in a previously healthy person, the disease is classified as primary, while patients with concomitant systemic autoimmune diseases (SAD) are classified as associated (or secondary) SjS; since this distinction only reflects a clinical situation of autoimmune coexistence the term SjS will be throughout the manuscript. SjS patients make substantial use of healthcare services, with a mean annual total direct cost per patient ranging between £2200 in UK and US$20 000 in the USA.[4 5]

The therapeutic management of SjS has not changed substantially in recent decades[6] and is still based on symptomatic treatment of sicca

two patient representatives. The SC agreed on some principal considerations upfront: (a) The statements were termed 'recommendations' as opposed to 'guidelines' or 'points to consider' because they offer guidance, which needs to be tailored to meet individual requirements. (b) Some general rules and definitions (overarching principles, general recommendations, definition of sequential therapeutic schedules, severity or refractoriness) cannot be evidence-based and were, therefore based on consensus. (c) The remaining statements were evidence-based, that is, supported by the highest level of evidence possible, limiting statements based only on retrospective data (although for some clinical or therapeutic scenarios with no data in controlled studies, this was allowed if the amount of retrospective data was considered significant and scientifically reliable); recommendations based on data obtained from case reports were not allowed. (d) Evidence was collected from studies including primary SjS patients fulfilling the 2002/2016 criteria (SjS-2002).[15 16] When no evidence was available, evidence from studies including associated SjS, patients fulfilling previous sets of criteria or those including a mix of autoimmune and non-autoimmune aetiologies was considered and extrapolated (online supplementary table S1). (e) The balance between efficacy and side effects was evaluated agent by agent. (f) Although recommendations are primarily supported by the evidence reported in patients with primary SjS, the advice on topical and systemic

- SC öncelikle bazı prensipler üzerinde hemfikir olmuş
  a. «recommendation» terimi benimsenmiş
  b. Bazı genel kurallar (overarching principles) kanıta dayalı olamaz denmiş (consensus)
  c. Diğer öneriler kanıta dayalı
  d. Kanıtlar öncelikle 2002/2016 sınıflaması ile yapılan çalışmalardan gelmiş (yoksa öncekilerden)
  e. Etki/yan etki dengesi her ajan için ayrı belirlenmiş
  f. Öneriler primer Sj için yapılsa da sekonder olgulara da extrapole edilebilir denilmiş

Table 1 Overarching (A–C) and specific (1–12) recommendations

	LoE	GoR	Vote (%)	LoA (0–10)
A.Patients with SjS should be managed at, or in close collaboration with, centres of expertise following a multidisciplinary approach	NA	NA	90	9.2
B.The first therapeutic approach for dryness should be symptomatic relief using topical therapies	NA	NA	93	8.9
C.Systemic therapies may be considered for the treatment of active systemic disease	NA	NA	90	9.1

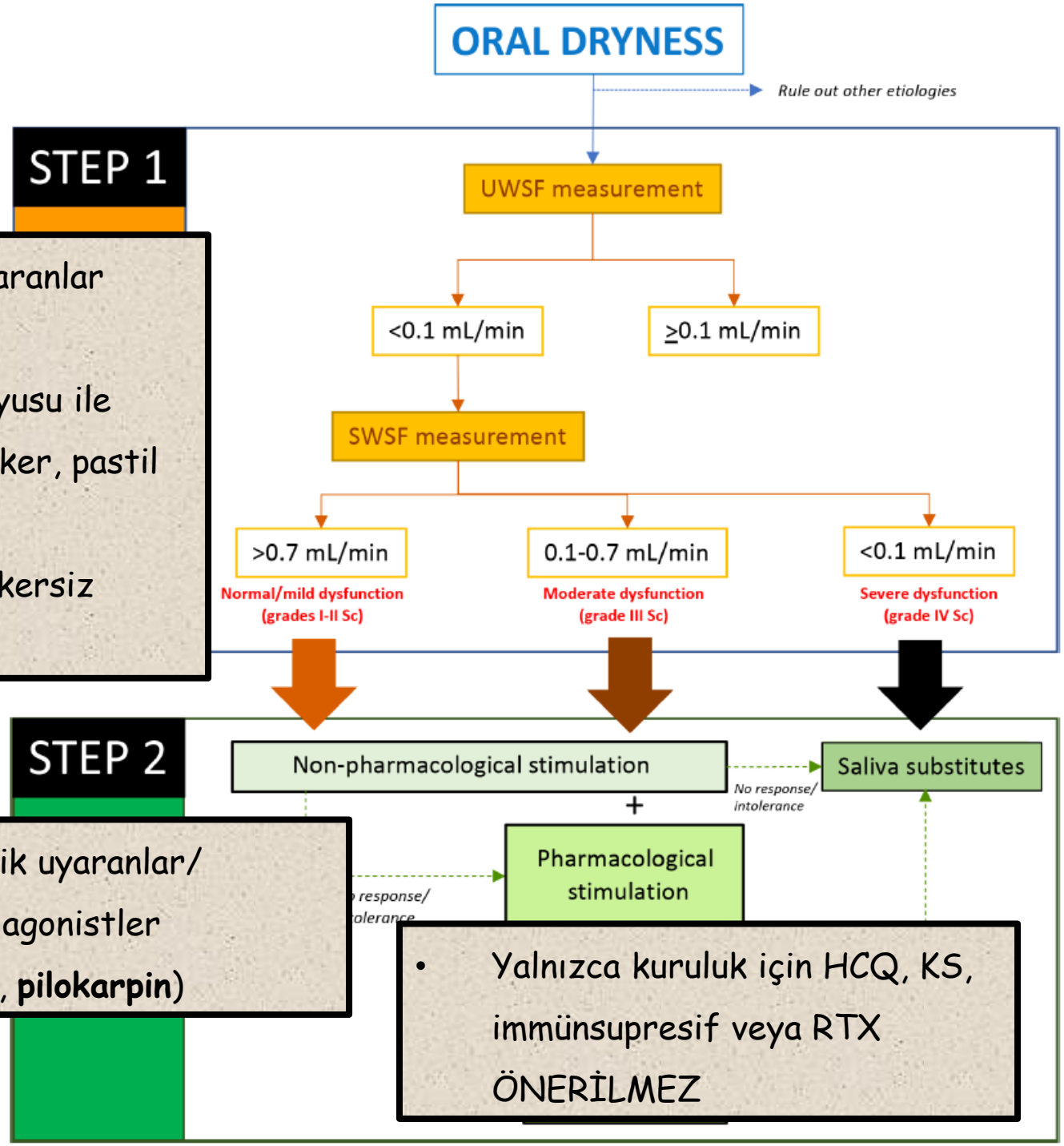
A. Sj hastaları bu konuda uzmanlaşmış merkezlerde (!) mulidisipline yaklaşımla yönetilmelidir
B. İlk tedavi yaklaşımı kuruluğu semptomatik iyileştirecek topikal tedavilerle olmalı
C. Aktif sistemik hastalığı olanlarda sistemik tedaviler **düşünülebilir**

- SjS'nun hem semptomları (kuruluk, yorgunluk ve ağrı üçlüsü), hem ciddi sistemik tutulumu hem de lenfoma nedeniyle artmış mortalitesi nedeniyle QoL üzerine önemli etkisi vurgulanmış

- Glandular disfonksiyonu geri döndüren tedavi yok, yani kuruluğu ortadan kaldıramayağınız için günlük semptomatik tedavi

1.Baseline evaluation of salivary
2.The preferred first therapeutic a
2.1. Non-pharmacological stim
2.2. Pharmacological stimulati
2.3. Saliva substitution for sev

- Nonfarmakolojik uyaranlar (kanıtı yok;
  - Tat alma duyusu ile (şekersiz şeker, pastil ve xylitol)
  - Mekanik (şekersiz ciklet

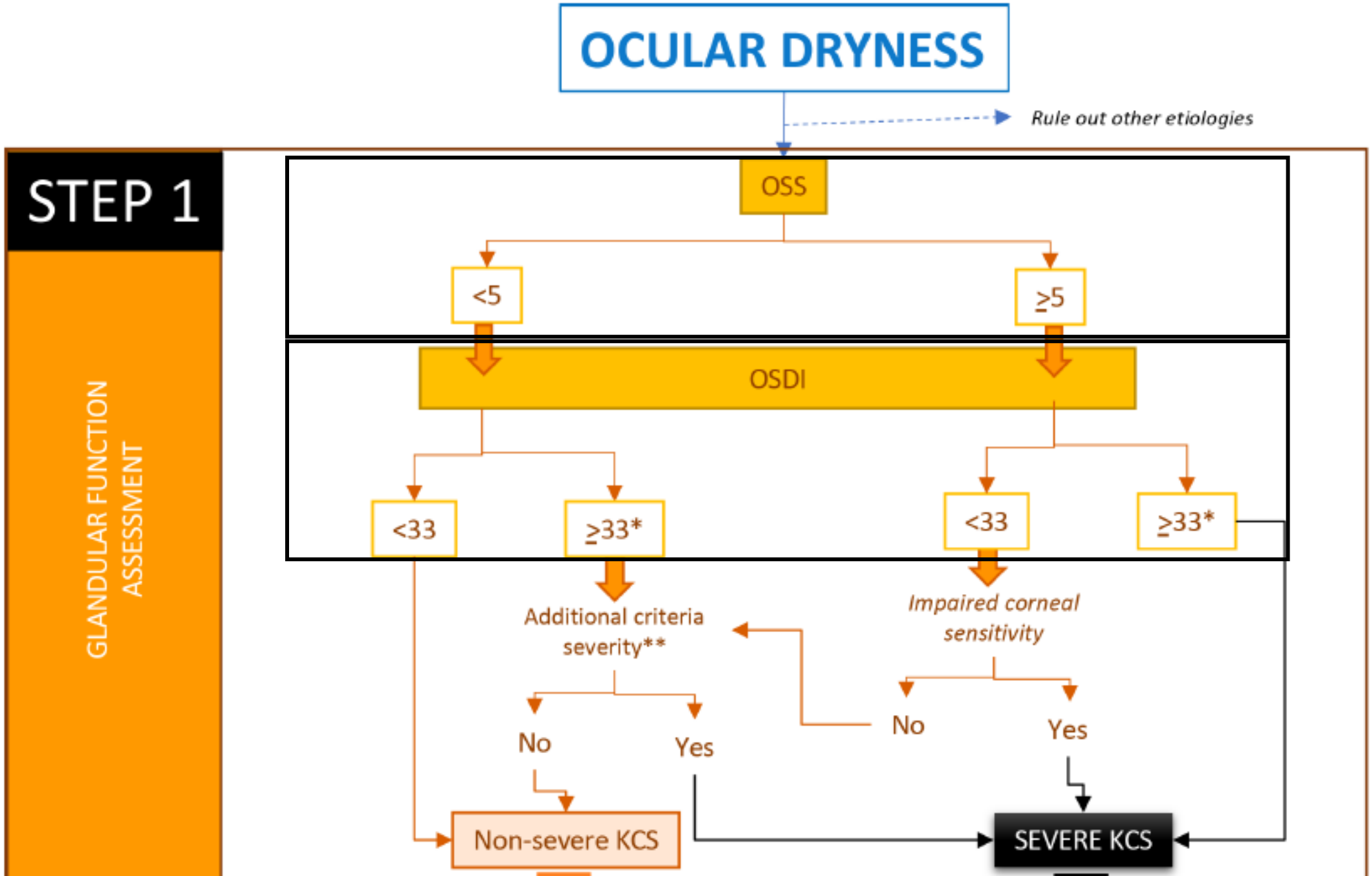


- Farmakolojik uyaranlar/ muskorinik agonistler (sevimeline, **pilokarpin**)

- Yalnızca kuruluk için HCQ, KS, immünsupresif veya RTX ÖNERİLMEZ

10.B-cell targeted therapies may
11.The systemic organ-specific th
immunosuppressive agents and
12.Treatmen

	5	D	81	8.7
	1a/*1b	B	88	8.7
	1a	B	98	9.5
e	1a/*1b	B/D	94	9.1
ic	5	D	93	9.0
and	4	C	89	8.9
	4	C	89	9.0
	4	C	85	9.6
er	4	C	82	8.9
	1b	B	98	8.6
	5	D	98	8.6
	4	C	88	9.7


OCULAR DRYNESS
Rule out other etiologies
STEP 1
GLANDULAR FUNCTION ASSESSMENT
OSS
<5
≥5
OSDI
<33
≥33*
<33
≥33*
Additional criteria severity**
No
Yes
Impaired corneal sensitivity
No
Yes
Non-severe KCS
SEVERE KCS

SICCA Ocular Staining Score

	Right Eye		Left Eye	
Staining pattern score:	Lissamine Green (conjunctiva only)	Fluorescein (cornea only)	Lissamine Green (conjunctiva only)	Fluorescein (cornea only)
	Grade / Dots	Grade / Dots	Grade / Dots	Grade / Dots
	0 / 0-9	0 / 0	0 / 0-9	0 / 0
	1 / 10-32	1 / 1-5	1 / 10-32	1 / 1-5
	2 / 33-100	2 / 6-30	2 / 33-100	2 / 6-30
	3 / >100	3 / >30	3 / >100	3 / >30
Extra points–fluorescein only: (Mark all that apply and add to fluorescein score)	☐ +1 - patches of confluent staining ☐ +1 - staining in pupillary area ☐ +1 - one or more filaments		☐ +1 - patches of confluent staining ☐ +1 - staining in pupillary area ☐ +1 - one or more filaments	
Total Ocular Staining score:	☐☐		☐☐	

Total ocular staining scores of 3 to 12 per eye assess the range of severity for keratoconjunctivitis sicca.

Figure 2. Sjögren's International Collaborative Clinical Alliance (SICCA) ocular staining score form

Whitcher107 JP, et al. Am J Ophthalmol. 2010;149:405–15
Baudouin C,108 et al. Br J Ophthalmol 2014;98:1168–1176

OSDI (Ocular Surface Disease Index)

Patient name: **Date of birth:** **Patient ID:**

Have you experienced any of the following during the last week?

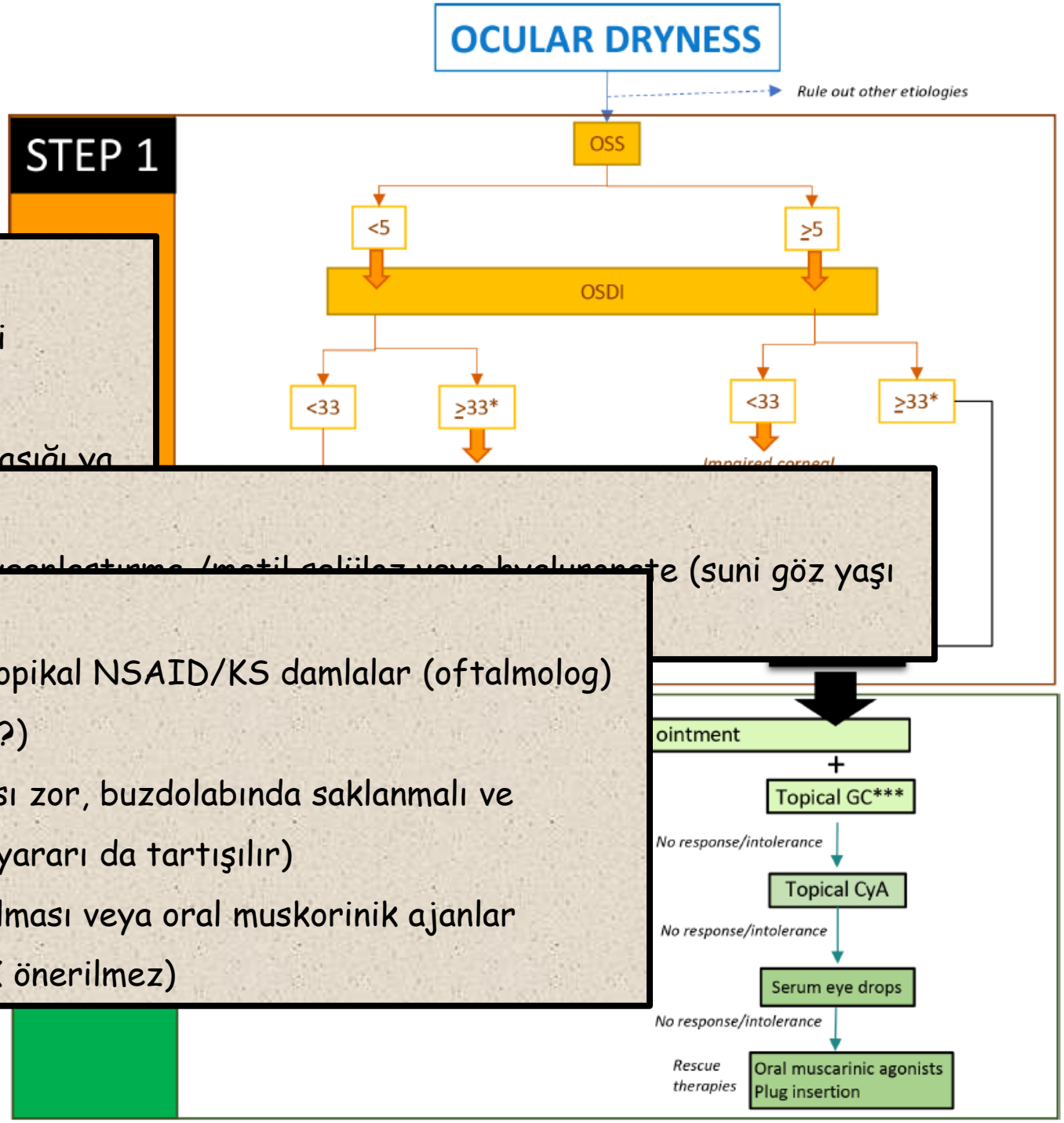
	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
1. Eyes that are sensitive to light?	☐	☐	☐	☐	☐	
2. Eyes that feel gritty?	☐	☐	☐	☐	☐	
3. Painful or sore eyes?	☐	☐	☐	☐	☐	
4. Blurred vision?	☐	☐	☐	☐	☐	
5. Poor vision?	☐	☐	☐	☐	☐	

Have you problems with your eyes limited you in performance any of the following during the last week?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	No Answer
6. Reading?	☐	☐	☐	☐	☐	☐
7. Driving at night?	☐	☐	☐	☐	☐	☐
8. Working with a computer or bank machine (ATM)?	☐	☐	☐	☐	☐	☐
9. Watching TV?	☐	☐	☐	☐	☐	☐

Have your eyes felt uncomfortable in any of the following situations during last week?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	No Answer
10. Windy conditions?	☐	☐	☐	☐	☐	☐
11. Places or areas with low humidity (very dry)?	☐	☐	☐	☐	☐	☐
12. Areas that are air conditioned?	☐	☐	☐	☐	☐	☐



Ek ciddiyet kriterleri;

1. Görme fonk yetersizliği
2. Bleferospazm
3. Ciddi meybom bez hastaşığı ya

İlk sıra tedavi:

- Yalıma preparatları ve kayganlaştırma (metil selüloz veya hyaluronate (suni göz yaşı

Refrakter göz kuruluğunda:

- 2-4 haftalık kısa süreli topikal NSAID/KS damlalar (oftalmolog)
- Topikal CsA (takrolimus??)
- Otolog serum (hazırlaması zor, buzdolabında saklanmalı ve kontaminasyon riski var, yararı da tartışılır)
- Rescue amaçlı; tıkaç takılması veya oral muskorinik ajanlar
- HCQ, IS, oral KS ve RTX önerilmez)

Halsizlik, yorgunluk ile başvuran hastalarda:

- OA, hipotiroidi/hipokortizolizm, vit defektleri, depresyon, tm vb konkomitan hastalık
- Sj sistemik komplikasyonları (artrit, anemi, hiokalemi, osteomalazi, lenfoma vb) akılda tutulmalıdır
- Ayrıca somatik fonksiyonel sendromlar (FMS, kronik yorgunluk send) hatırlanmalı

tools				
6.Consider analgesics or other pain-modifying agents for musculoskeletal pain, considering the balance between potential benefits and side-effects	4	C	89	8.9

Kas iskelet sistemi ağrılarında

- Akut ağrılarda asetaminofen/NSAID 7-10 gün
- Sık akut ağrı epizotlarında SLE gibi HCQ (RTX ve ANA çalışmaları off label biolojik kullanımını desteklememiş
- Kronik hergün noninflamatuvar ağrı varsa pregabalin, gabapentin, amitriptilin, anti-depresanlar tekrarlayan NSAID kullanımına engel olabilir. Opiodler KULLANILMAMALIDIR

1.Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness	5	D	81	8.7
2.The preferred first therapeutic approach for oral dryness according to salivary gland function may be:	1a/*1b	B	88	8.7
2.1. Non-pharmacological stimulation for mild dysfunction;				
2.2. Pharmacological stimulation* for moderate dysfunction;				
2.3. Saliva substitution for severe dysfunction				
3.The first-line therapeutic approach to ocular dryness includes the use of artificial tears and ocular gels/ointments	1a	B	98	9.5
4.Refractory/severe ocular dryness may be managed using topical immunosuppressive-containing drops* and autologous serum eye	1a/*1b	B/D	94	9.1
side-effects				
7.Treatment of systemic disease should be tailored to organ-specific severity using the ESSDAI definitions	4	C	89	9.0
8.Glucocorticoids should be used at the minimum dose and length of time necessary to control active systemic disease	4	C	85	9.6
9.Immunosuppressive agents should be mainly used as GC-sparing agents, with no evidence supporting the choice of one agent over another	4	C	82	8.9
10.B-cell targeted therapies may be considered in patients with severe, refractory systemic disease	1b	B	98	8.6
11.The systemic organ-specific therapeutic approach may follow, as a general rule, the sequential (or combined) use of GCs, immunosuppressive agents and biologics	5	D	98	8.6
12.Treatment of B-cell lymphoma should be individualised according to the specific histological subtype and disease stage	4	C	88	9.7

Sistemik hastalık yönetimi ESSDAI temelinde yapılan tanımlamalara göre organ spesifik şiddetine uygun olmalı

Table 2 Glossary and definitions

Term	Definition	Examples
1.Nomenclature of therapies	1.1. Interventions directly applied to the mucosal surfaces involved	1.1. Saliva substitutes, ocular tears
1.1. Topical therapies	1.2. Drugs administered orally or intravenously for systemic disease	1.2. Antimalarials, glucocorticoids, immunosuppressive agents, intravenous immunoglobulins, biologics
1.2. Systemic therapies		
2.Disease activity terms	2.1. Disease involvement that affects or has affected any of the organs/systems included in the clinESSDAI score	2.1. All ESSDAI domains except biological domain
2.1. Systemic disease	2.2. Patients with clinESSDAI score ≥1.	2.2. Systemic activity is classified as low if ESSDAI is 1–4 (if not only due to biological domain), moderate between 5–13 and high ≥14.
2.2. Active systemic disease	2.3. Patients with ESSDAI score >14, or high activity in any of the ESSDAI domains with a definition of high activity	2.3. Lymphadenopathy and lymphoma, articular, cutaneous, pulmonary, renal, muscular central and peripheral neurological and haematological domains.
2.3. Severe systemic disease	2.4. Systemic manifestation/s refractory to SOC.	2.4. Due to the diversity of systemic manifestations, SOC (first-line therapeutic approach) has been defined for each systemic manifestation (figure 3)
2.4. Refractory systemic disease	2.5. Decrease of ≥3 points in the global ESSDAI score	–
2.5. Therapeutic response		
	scores.	
4.Recommended instruments of measure	4.1. UWSF, SWSF	
4.1. Salivary gland function	4.2. OSS, OSDI	
4.2. Corneal damage	4.3. ESSPRI domains, ProFAD	
4.3. Fatigue	4.4. ESSPRI domains, BPI	
4.4. Pain	4.5. ESSPRI	
4.5. Quality of life	4.6. ESSDAI, clinESSDAI	
4.6. Systemic disease		
5.Potential life-threatening systemic manifestations	5.1. Cutaneous domain	5.1. Diffuse vasculitis with ulcers
	5.2. Pulmonary domain	5.2. ILD with NHYA III/IV
	5.3. Renal domain	5.3. Renal failure; rapidly-progressive glomerulonephritis; hypokalaemic paralysis
	5.4. Muscular domain	5.4. Muscular involvement with severe weakness
	5.5. Peripheral nerve system domain	5.5. Neuropathy (including ganglionopathy and polyradiculopathies) with severe motor deficit/ataxia; cryoglobulinemic-related multineuritis
	5.6. CNS domain	5.6. Demyelinating disease with motor deficit; cerebral vasculitis presenting with focal deficit; myelitis; meningoencephalitis
	5.7. Haematological domain	5.7. Severe haemolytic anaemia (<80 g/dL, <50 x109/L); severe autoimmune thrombocytopenia (<50 000/mm3)

Sistemik tedaviler en azından orta ESSDAI skoru (>5) olanlarda gündeme gelmeli ve yanıt ESSDAI skorunun en az 3 puan gerilemesi olarak tanımlanıyor

Şiddetli refrakter sistemik hastalığı olan Sj hastalarında B hücre hedefli tedaviler düşünülebilir

İmmünsupresifler GS-sparing amaçlı kullanılmalıdır ama birinin diğerine göre daha iyi olduğunu gösteren kanıt bulunmamaktadır

GC'ler sistemik hastalık kontrolü için minumum doz ve sürede kullanılmalı

tools				
6.Consider analgesics or other pain-modifying agents for musculoskeletal pain, considering the balance between potential benefits and side-effects	4	C	89	8.9
7.Treatment of systemic disease should be tailored to organ-specific severity using the ESSDAI definitions	4	C	89	9.0
8.Glucocorticoids should be used at the minimum dose and length of time necessary to control active systemic disease	4	C	85	9.6
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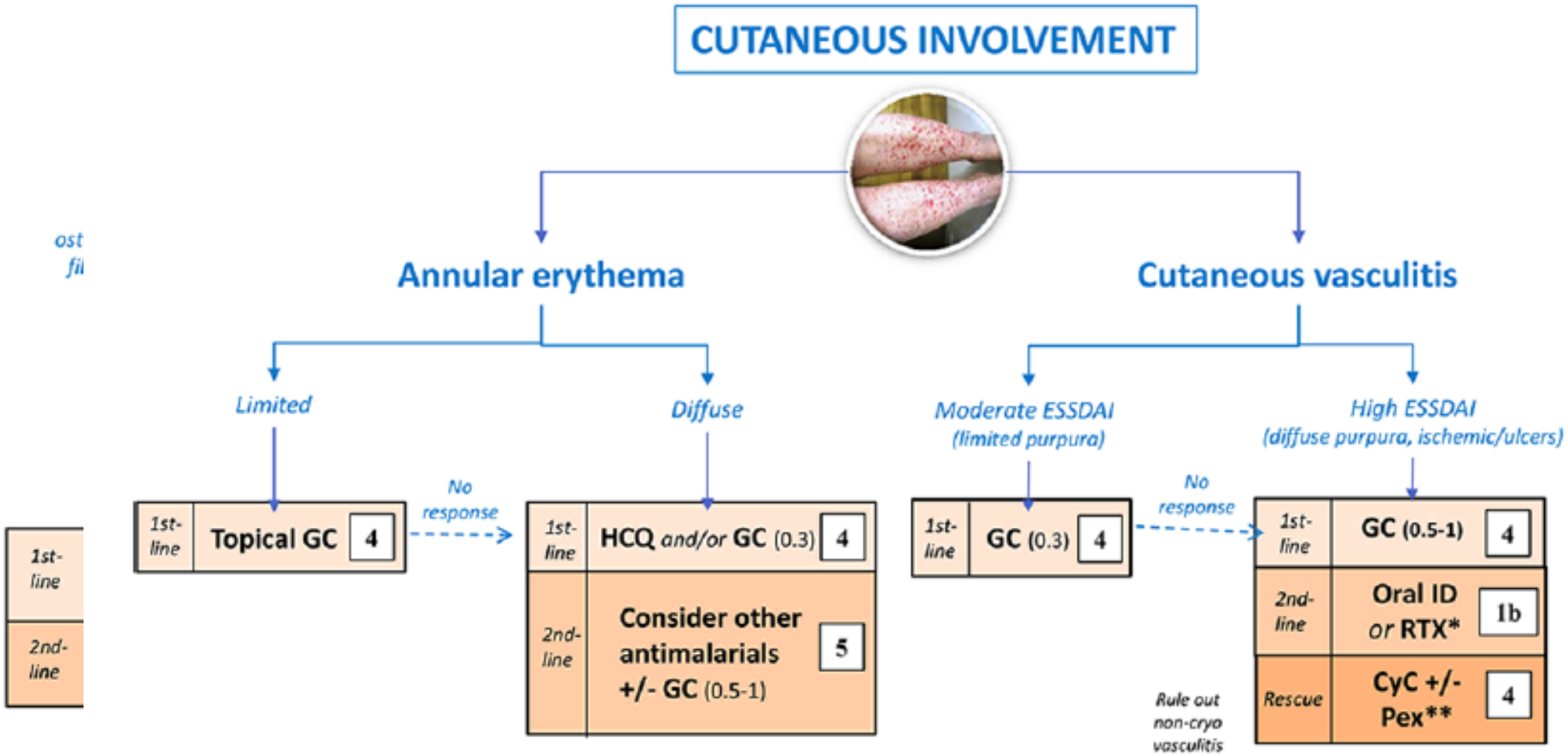
Sistemik organ spesifik tedavi yaklaşımı izlenebilir ve genel bir kural olarak GC, immünsupresif ve biolojikler sekansiyel veya kombine kullanılabilir (her ne kadar kontrollü çalışması olmasa da)

A B C



*Cryo vasculitis
**Life-threatening cryo vasculitis

D E F

Bron

1st-line

1st-line S

PERIPHERAL NEUROPATHY

Rule out non-cryo vasculitis

Multineuritis

1st-line	GC (0.5-1)	4
2nd-line	Oral ID *or* RTX*	4
Rescue	CyC +/- Pex**	4

Vasculitis-related

Axonal PN

Sensory

1st-line	Symptomatic***	4

Motor

No response

Ganglionopathy

CIPD

1st-line	ivIG	4
2nd-line	Consider pulses MP	5
Rescue	Consider CyC	5

*Symptoma

*Cryo vasculitis

**Life-threatening cryo vasculitis

***control neurological pain + cardiovascular risk factors

G H I

Ro+ Sjögren women of reproductive age

LoE 3b — Consider primary prevention with HCQ

LoE 2b — Consider secondary prevention with HCQ

Consider use of home monitoring for fetal heart rythm — LoE 2b

CHB

Incomplete (1st degree)

Consider Fluorinated GC* — 5

*Repeat echo next day

Incomplete (2nd degree)

1st-line	Start Fluorinated GC**	4
2nd-line	Consider adding ivIG	4

**Short-time use (1 month)

If uncertain as to whether abnormal rate and/or rhythm are due to incomplete or complete block

Complete (3rd degree)

Confirmed diagnosis

EFE, hydrops, poor function

Continue to monitor for

Yes

1st-line	Fluo GC + IVIG	4
2nd-line	Consider Pex	4

No

No indication for Fluorinated GC — 3b

No indication for IVIG — 2b

No indication for plasmapheresis — 2b

1.Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness	5	D	81	8.7
2.The preferred first therapeutic approach for oral dryness according to salivary gland function may be:	1a/*1b	B	88	8.7
2.1. Non-pharmacological stimulation for mild dysfunction;				
2.2. Pharmacological stimulation* for moderate dysfunction;				
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11.The systemic organ-specific therapeutic approach may follow, as a general rule, the sequential (or combined) use of GCs, immunosuppressive agents and biologics	5	D	98	8.6
12.Treatment of B-cell lymphoma should be individualised according to the specific histological subtype and disease stage	4	C	88	9.7

- Sj'lu hastalarda lenfoma insidans ratio (popülasyon ile kıyaslanınca) 7-9, hastane çalışmalarında 16-48 bildiriliyor
- Çoğu (15x) B hc tipinde
- Çoğu MALT, marjinal zon ve Diffüz büyük B hc'li
- Sonuç olarak B hüc lenfomalarının tedavisi spesifik histolojiye ve hastalık evreseine göre bireyselleştirilmelidir deniliyor

Box 1 Research agenda

- Is there a specific, differentiated treatment of lymphomas related to SjS?
- Is combination therapy a potential intervention to explore in SjS?
- Exploring targeted therapies against Th17 cytokines, IFNα, RORγt expression, Janus kinases (JAKS), STATs and mTOR intracellular pathways or interleukin-1.
- Searching for predictive factors of biological response.
- Potential use of sequential or intralesional use of biological therapies.
- Encouraging the development of new and innovative therapies.
- In what proportion of systemic patients is induction therapy with current therapeutic options effective in inducing sustained remission?
- Is the use of immunosuppressive and biologic agents safe and efficacious in the absence of concomitant glucocorticoid treatment?
- How safe and efficacious is the off-label use of other biologics after rituximab has failed?
- Can we find predictors of differential response to the synthetic and biological drugs used in SjS?
- Can we predict who will maintain remission after withdrawal of glucocorticoids?
- Will we be able to develop precision (personalised, stratified) medicine approaches in SjS? (IFN signature +/-; immunological or histopathological markers +/-)?
- Which biomarkers will help identify better predictors of poor outcomes?

- Sj ilişkili lenfomaların spesifik farklı bir tedavisi olabilir mi?
- Kombinasyon tedavisi potansiyel bir alternatif olabilir mi?
- Th17, Jak,
- IFN, mTOR ve IL-1 vb yolaklar çalışıyor mu?
- Biolojik yanıt öngörülebilir mi?
- Biolojikler sekansiyel veya intralezyonel kullanılabşilir mi?
- Yeni/yenilikçi tedaviler var mı?
- İndüksiyon tedavisi ile ne kadar kalıcı remisyon sağlanıyor?
- RTX IR hastalarda diğer biyolojikler ne kadar etkili/güvenilir?
- Biyolojiklerin ve sentetiklerin yanıt farklarını predikte edebilir miyiz?
- Tedaviyi bireyselleiştirebilir miyiz?
- ……
- ……
- ….

TEŞEKKÜRLER