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Nieuwe Behandeling bij patiënten met het syndroom van Sjögren
Hot&New

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Sjögren's Syndrome

Behandeling

- Lokale symptoombestrijding

- Systemische behandeling kan worden overwogen bij actieve, systemische ziekte met orgaan-betrokkenheid

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Symptomatische behandeling sicca

- Ogen
  - Oogdruppels, vb. hylan, artelac
  - Ooggel, vb. vidisic (zonder conserveermiddelen)
  - Dexamethason oogdruppels, Ciclosporine oogdruppels
- Mond
  - Stimulatie van speeksel: suikervrije snoepjes, Xylimelts
  - Mondgel, kunstspeeksel, mondsprays
  - Pilocarpine
- Vaginale droogheidsklachten
  - Hyalofemme
- Huid
  - Indifferente middelen: Groninger bad/douche olie, cetomacrogol etc.

Symptomatische behandeling

- Speekselklierzwelling
  - Speekselkliermassage adviseren
  - Soms NSAIDs
  - In geval van bacteriële speekselklierontsteking: antibiotica (tenminste 10-14 dagen)
- Tendinomyalgie of artralgie
  - Paracetamol
  - NSAIDs

Immunosuppressieve behandeling

- Conventionele DMARDs
  - Cyclofosfamide
    - Bij: PNS of CNS betrokkenheid, renale betrokkenheid
  - MTX
    - Bij: artralgie of artritis, secundaire SS
    - Kans op B-cel hyperactiviteit

Immunosuppressieve behandeling

- Conventionele DMARDs
  - Hydroxychloroquine
    - Onderzocht in JOQUER trial*, geen effectiviteit op primair eindpunt (verbetering in droogte, vermoeidheid, pijn)
    - Bij: artralgie of artritis, cutane betrokkenheid
  - Leflunomide
    - Bij: artralgie of artritis, cutane betrokkenheid
  - MMF
    - Bij: pulmonale betrokkenheid, PNS betrokkenheid, renale betrokkenheid
  - Combinatie HCQ/LEF, of HCQ/MMF
    - HCQ/LEF bleek effectief in RepurpSS-I (kleine, fase 2 RCT)**

**Gottenberg et al, JAMA 2014*
***van der Heijde et al, Lancet Rheum 2020*

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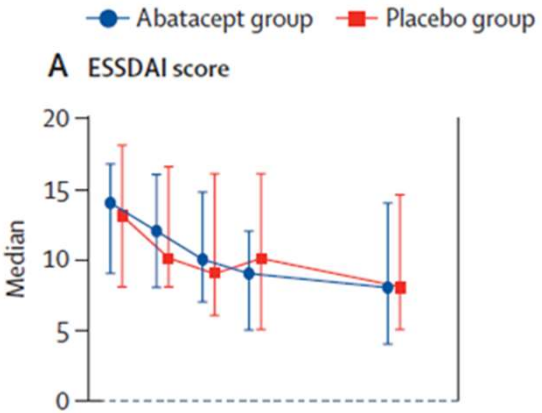
Immunosuppressieve behandeling

- Biological DMARDs
  - Rituximab (anti-CD20)
    - Twee grote RCTs (TRACTISS* en TEARS trial**) lieten geen effectiviteit zien op primair eindpunt (verbetering in droogte, vermoeidheid, pijn)
    - Bij: cutane vasculitis, pulmonale betrokkenheid, renale betrokkenheid, PNS of CNS betrokkenheid, ernstige hematologische betrokkenheid
  - Abatacept (remt costimulatie door binding aan CD80- en CD86)
    - Twee grote RCTs (ASAP-III in UMCG*** en multinationale trial****) lieten geen effectiviteit zien op primair eindpunt (ESSDAI)
    - Bij: artritis, of combinatie van systemische betrokkenheid zoals constitutioneel, glandulaire activiteit en artritis



ASAP-III trial

*Bowman et al, A&R 2017
**Devauchelle et al, Ann Int Med 2014
***van Nimwegen et al, Lancet Rheum 2020
****Baer et al, Ann Rheum Dis 2020

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Behandeling van MALT lymfoom

- Expectatief beleid
  - Bij MALT gelimiteerd tot speekselklier zonder systemische activiteit
- Radiotherapie
- RCP-kuren

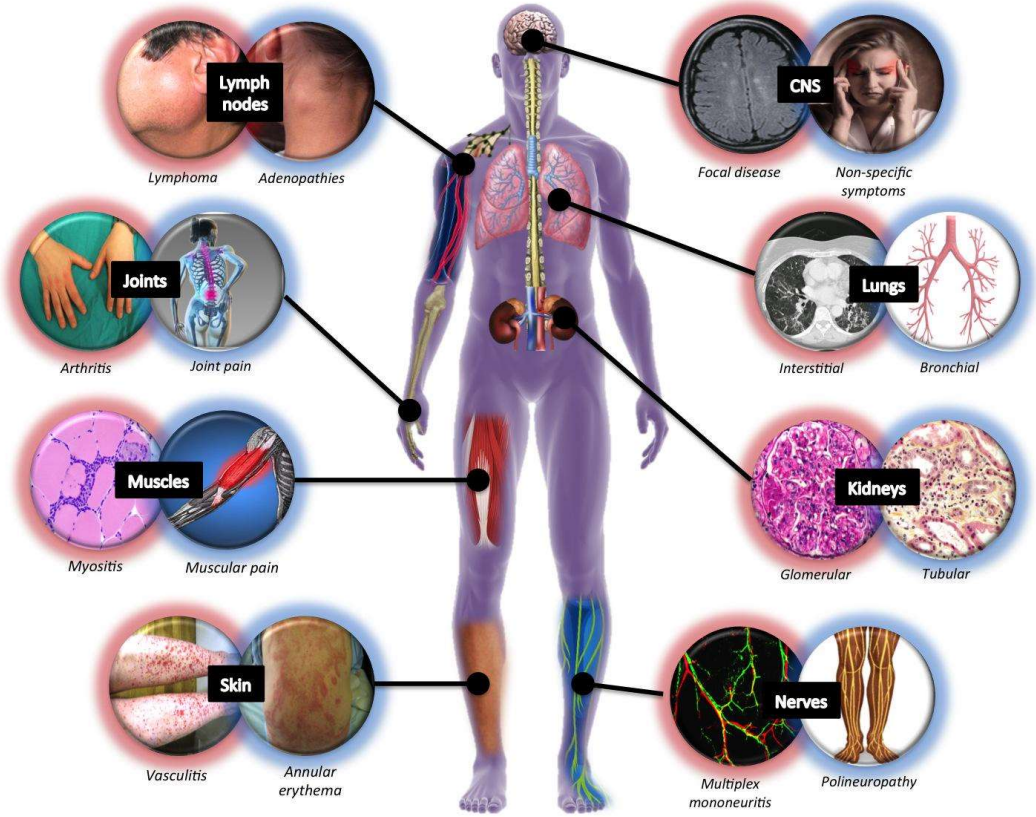
Meten van effectiviteit in RCTs

- Heterogene ziekte: welke uitkomstmaten gebruik je als primair eindpunt?

Uitkomstmaten bij pSS

- Systemische ziekteactiviteit: (Clin)ESSDAI

Domain	ESSDAI	ClinESSDAI
Constitutional (0–2)	3	4
Lymphadenopathy (0–3)	4	4
Glandular (0–2)	2	2
Articular (0–3)	2	3
Cutaneous (0–3)	3	3
Pulmonary (0–3)	5	6
Renal (0–3)	5	6
Muscular (0–3)	6	7
Peripheral nervous system (0–3)	5	5
Central nervous system (0–3)	5	5
Haematological (0–3)	2	2
Biological (0–2)	1	
Score total	0–123	0–135



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Uitkomstmaten bij pSS

- Patiënt-gerapporteerd symptomen (PROMs)
  - ESSPRI
- Objective glandulaire testen
  - Traanklier: Schirmer's test, Ocular Staining Score (OSS)
  - Speekselklier: ongestimuleerde en gestimuleerde speekselflow, echo van de speekselklieren
- Lab
  - Totaal IgG, reumafactor (RF)

1) How severe has your **dryness** been during the last 2 weeks?

No dryness	0 1 2 3 4 5 6 7 8 9 10	Maximal imaginable dryness

2) How severe has your **fatigue** been during the last 2 weeks?

No fatigue	0 1 2 3 4 5 6 7 8 9 10	Maximum imaginable fatigue

3) How severe has your **pain** (joint or muscular pain, in your arms or legs) been during the last 2 weeks?

No pain	0 1 2 3 4 5 6 7 8 9 10	Maximal imaginable pain

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RCTs & eindpunten

2004-2018

Drug (target)	Number of patients (enrolled or aim)	Primary endpoint
Etanercept (TNF-α)	28	≥20% improvement in ≥2 of 3 domains (subjective and/or objective measures for oral and ocular dryness, and ESR and IgG) at week 12
Infliximab (TNF-α)	103	≥30% improvement in ≥2 of 3 VAS (joint pain, fatigue, dryness) at week 10
Rituximab (CD20)	17	≥20% improvement in fatigue VAS at week 24
Rituximab (CD20)	30	Change in SWS
HCQ (TLR signalling)	120	≥30% improvement in ≥2 of 3 NRS scales (dryness, fatigue, pain) at week 24
Anakinra (IL1)	26	Difference between groups in fatigue scores adjusted for baseline values at week 4
Rituximab (CD20)	120	≥30 mm improvement on 2 of 4 VAS (global disease activity, pain, fatigue, dryness) at week 24
Rituximab (CD20)	133	≥30% improvement in fatigue or oral dryness VAS at week 48
Baminercept (LTβR)	52	Change in SWS at week 24

- Eerdere trials gebruikten niet-gevalideerde eindpunten
- Focus op PROMs en speekselproductie
- Geen van deze trials liet effectiviteit zien in het primaire eindpunt

Arends et al, Clin Exp Rheum 2022

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RCTs & eindpunten

2019-2022

HCQ/LEF (T-cells and TLR signalling)	29	Change in ESSDAI at week 24
Tocilizumab (IL6)	110	≥3 points improvement in ESSDAI, no occurrence of moderate or high activity in a new ESSDAI domain and no worsening in physician GDA (≥1/10) at week 24
Abatacept (CTLA4)	80	Change in ESSDAI at week 24
Ianalumab (BAFF receptor)	27	Change in ESSDAI at week 12
Iscalimab (CD40)	44 (two cohorts)	Safety and change in ESSDAI at week 12
MEDI5872 (ICOSL)	32	Change in ESSDAI at week 14
Seletalisib (PI3K)	27	Change in ESSDAI at week 12
Belimumab/rituximab (BAFF/CD20)	86	Number of participants with (S)AEs at week 68
RO5459072 (cathepsine-S inhibitor)	75	≥3 points improvement in ESSDAI at week 12
CDZ173 (leniolisib) (PI3K-delta)	30	Safety and change in ESSPRI at week 12
Abatacept (CTLA4)	187	Change in ESSDAI at week 24
Ianalumab (BAFF receptor)	190	Change in ESSDAI at week 24
Filgotinib (JAK), laraplenib (SYK), tirabrutinib (BTK)	150	Composite endpoint of CRP and patient-reported VAS scores (global disease, pain, oral, ocular dryness, fatigue) at week 12

- Recentere trials gebruikten met name de ESSDAI als primair eindpunt
- De meeste van deze trials lieten geen effectiviteit zien
  - Groot placebo effect met ESSDAI (>50% responders)
- Sommige recente, kleinere RCTs lieten wel effectiviteit zien
  - HCQ/LEF
  - Ianalumab (BAFFr)
  - Iscalimab (CD40)
  - Remibrutinib (BTK)

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Arends et al, Clin Exp Rheum 2022

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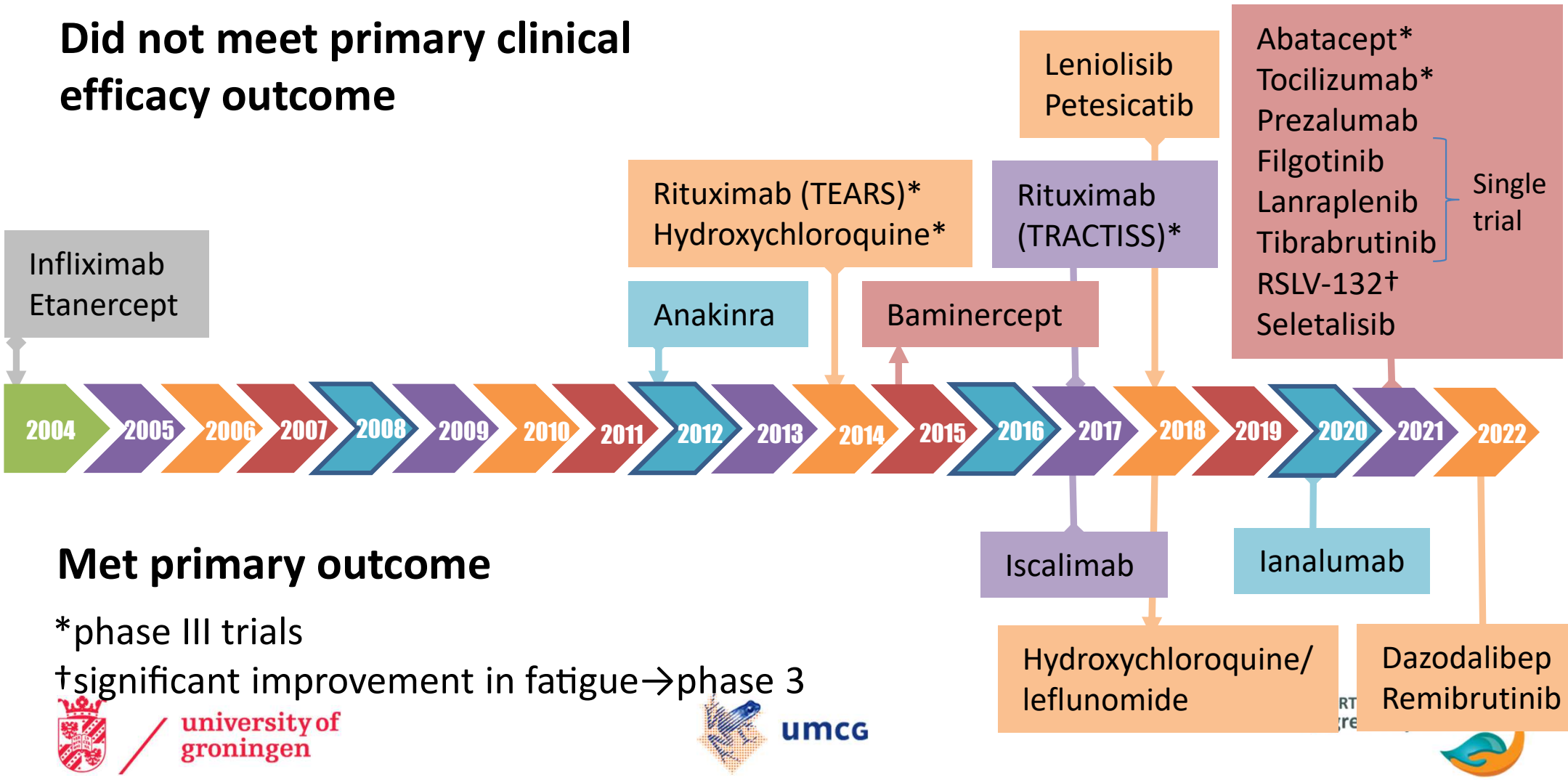
Placebo-controlled drug trials in Sjögren's



*phase III trials

†significant improvement in fatigue→phase 3

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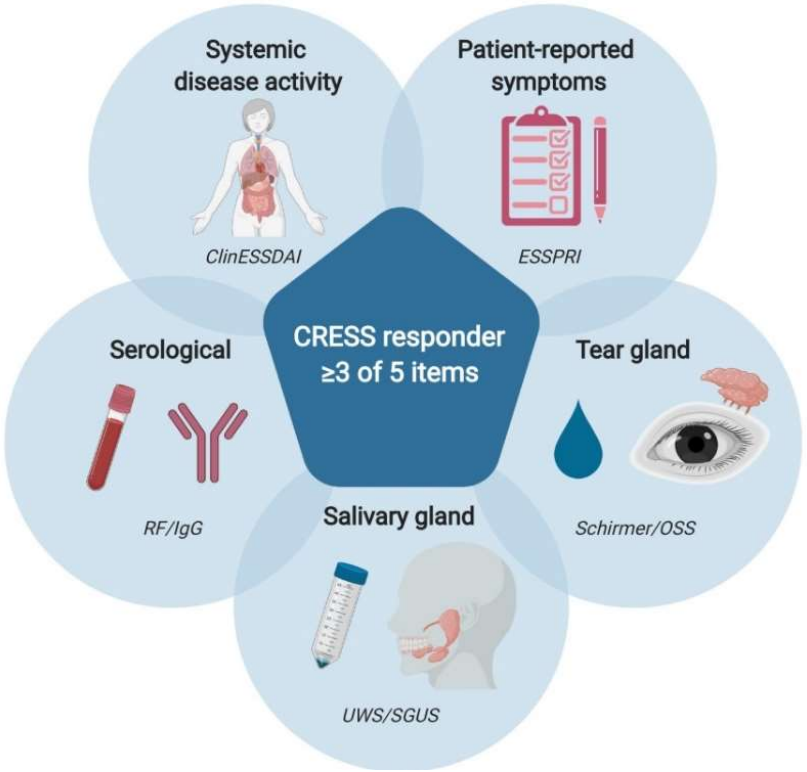
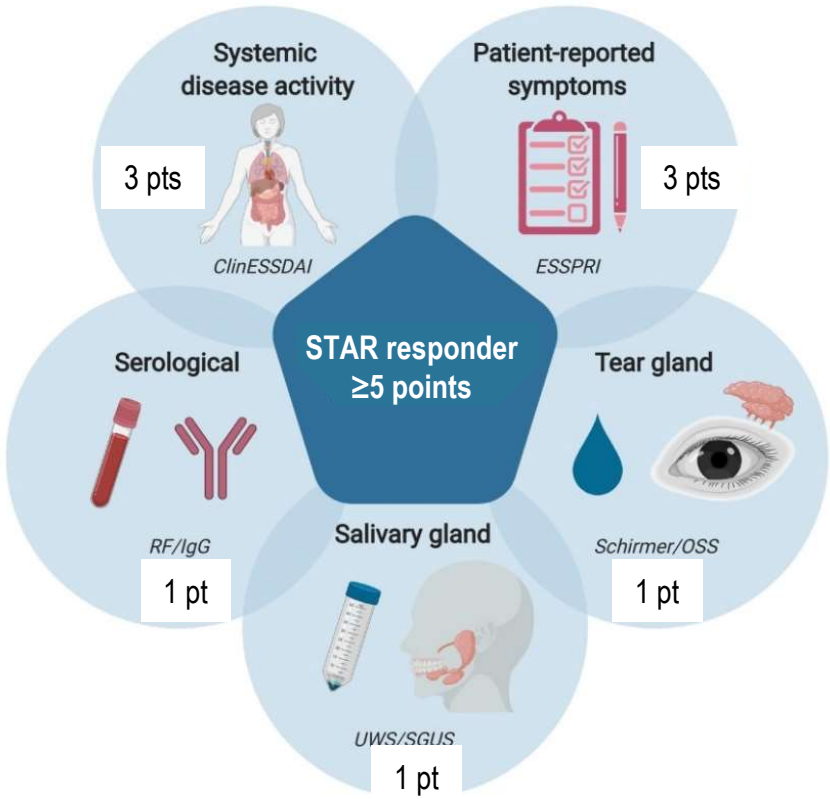
Nieuwe composite outcome measures voor trials in Sjögren's

CRESS



Systemic disease activity: clinESSDAI score <5

STAR



Systemic disease activity: Decrease of ≥3 in clinESSDAI

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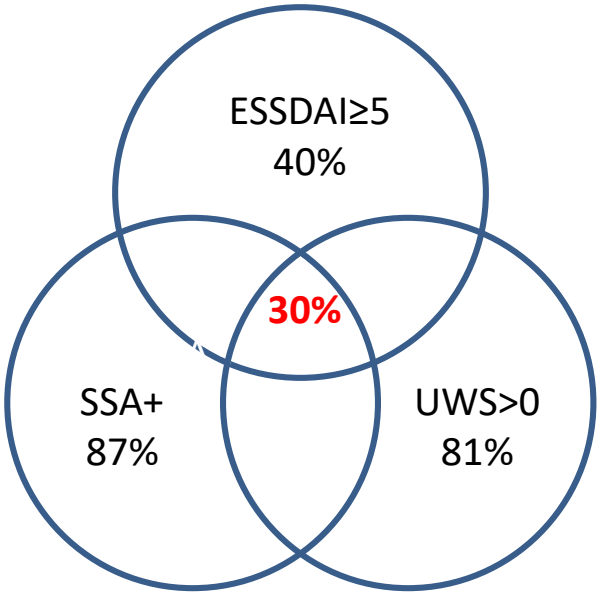
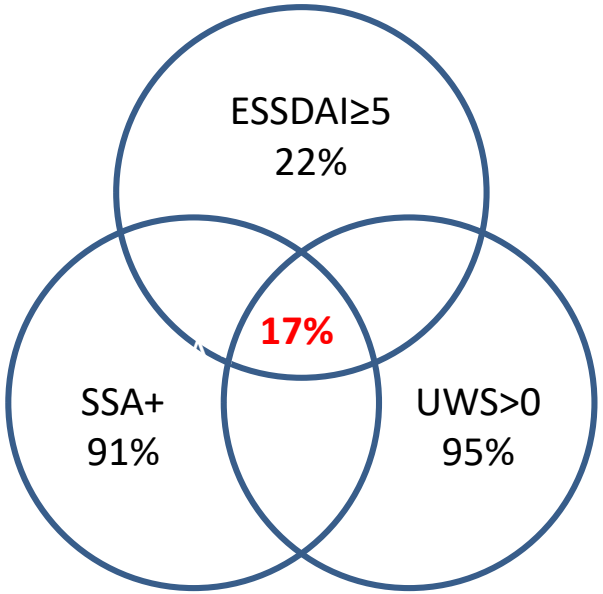
“Eligible” voor Sjögren trials



UWS=unstimulated whole saliva flow



RESULT cohort (Netherlands)
N=302

BeSSTT cohort (Belgium)
N=180

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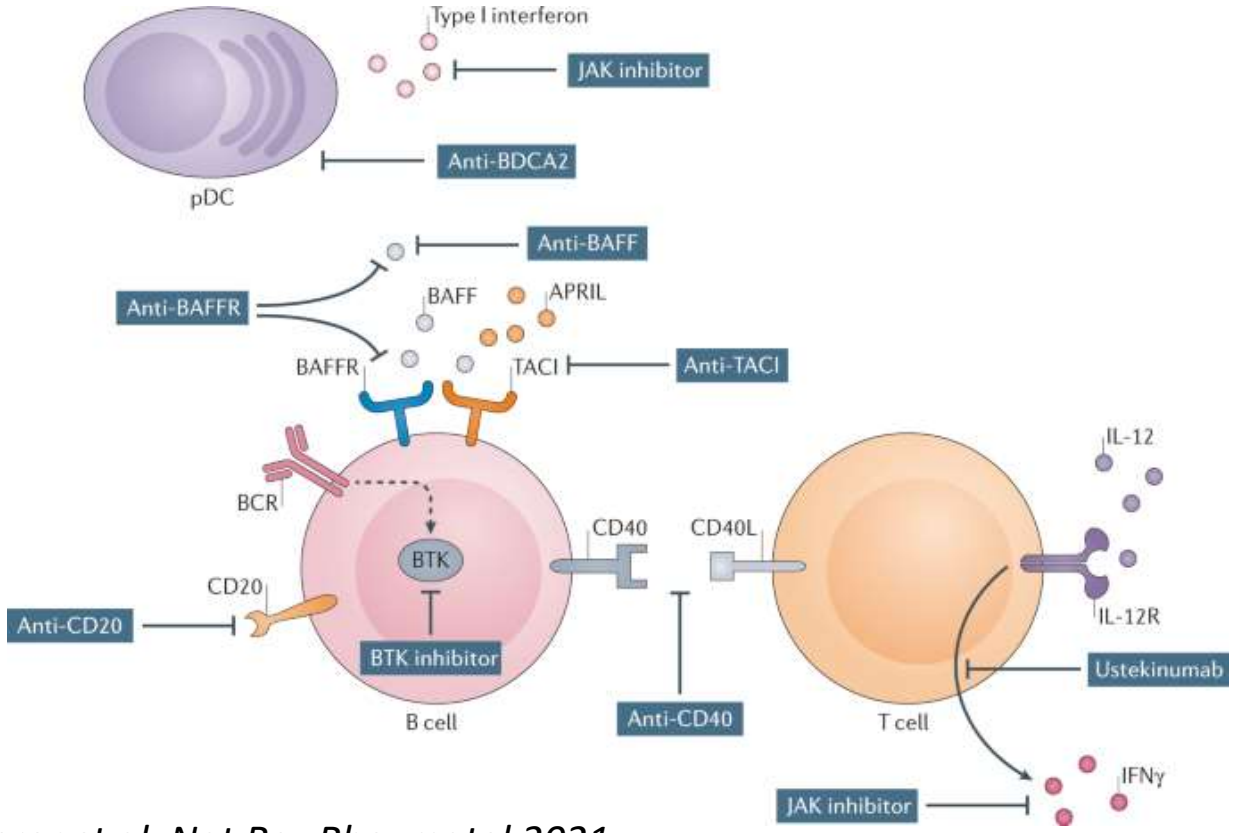
Arends et al, Clin Exp Rheumatol 2022, October 26

Nieuwe targets voor behandeling



Seror et al, Nat Rev Rheumatol 2021

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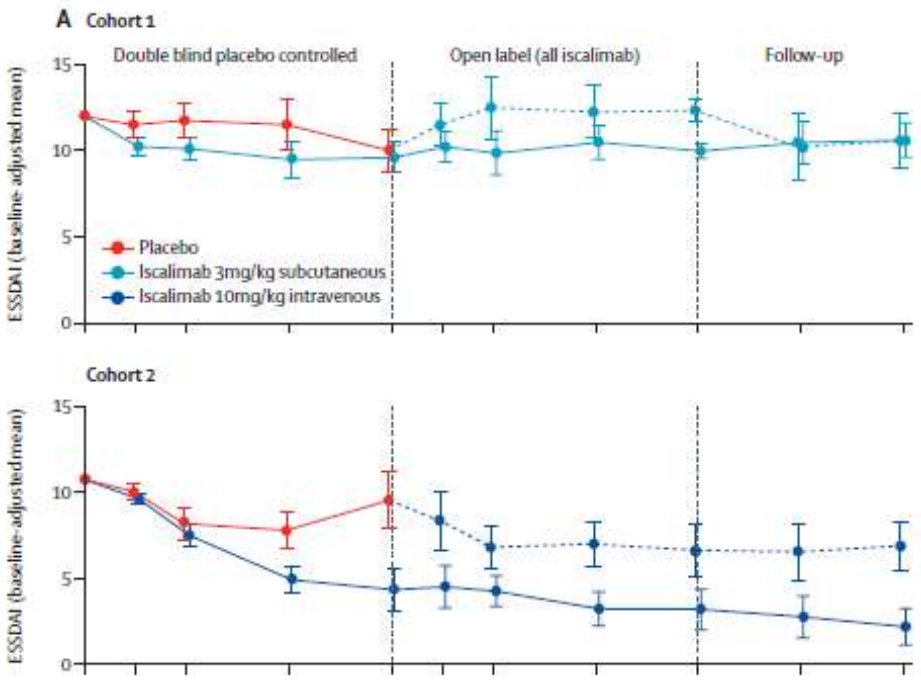
Recente trials

- Iscalimab (anti-CD40)
  - Fase 2 RCT in 44 patiënten (twee cohorten, verschillende doseringen), significante verbetering in ESSDAI vergeleken met placebo*
  - Fase 3 RCT momenteel gaande (TWINSS studie)
- Ianalumab (anti-BAFF receptor)
  - Fase 2a** en 2b*** RCT lieten verbetering zien in ESSDAI



*Fisher et al, Lancet Rheumatol 2020
**Dörner et al, Ann Rheum Dis 2019
*** Bowman et al, Lancet 2022

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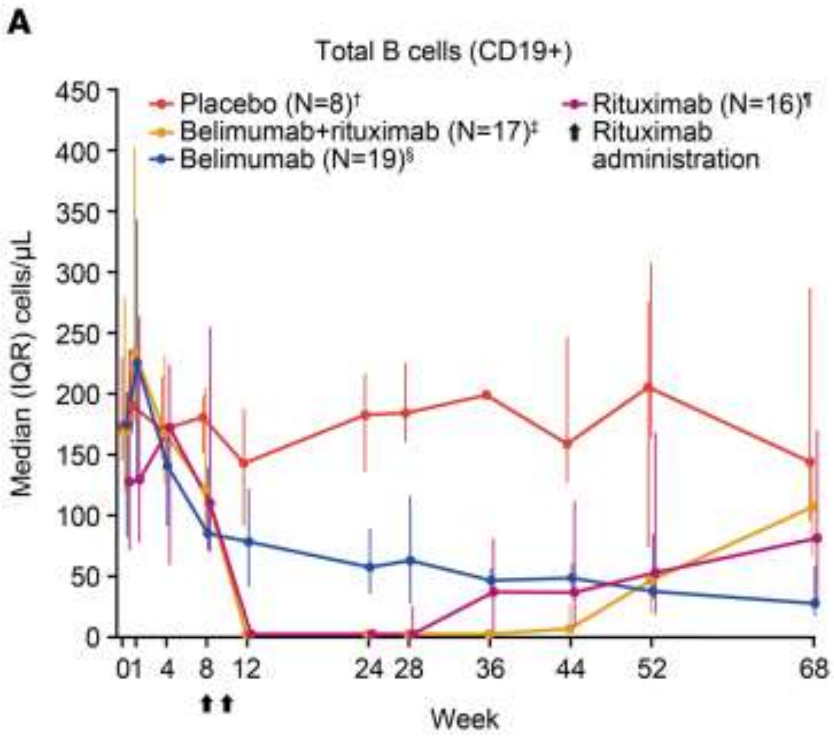
Recente trials

- Belimumab/rituximab combinatie
  - Fase 2 RCT met belimumab+rituximab* liet depletie zien van B-cellen in speekselklierbiopten, en afname van ESSDAI
  - CRESS responders: BEL + RTX



Mariette et al, JCI Insight 2020

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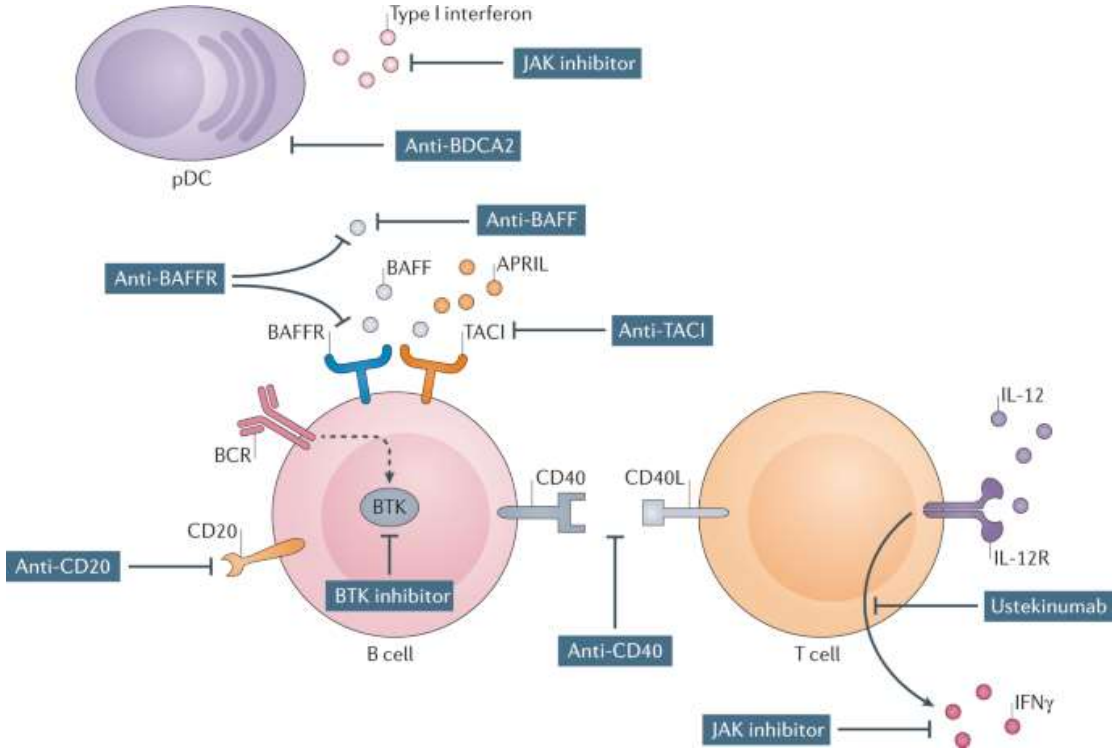
Recente trials

- Remibrutinib (BTK inhibitor)
  - RCT in 73 pSS patiënten* liet een significante verbetering in ESSDAI, speekselproductie en IgG zien
- Filgotinib (JAK inhibitor)
  - RCT met filgotinib, tirabrutinib (BTKi), lanraplenib (SYKi)** liet geen effectiviteit zien op primair eindpunt (combinatie van CRP en PROs)



Dörner et al, ACR 2022 abstract number 1113
***Price et al, Rheumatology 2022*

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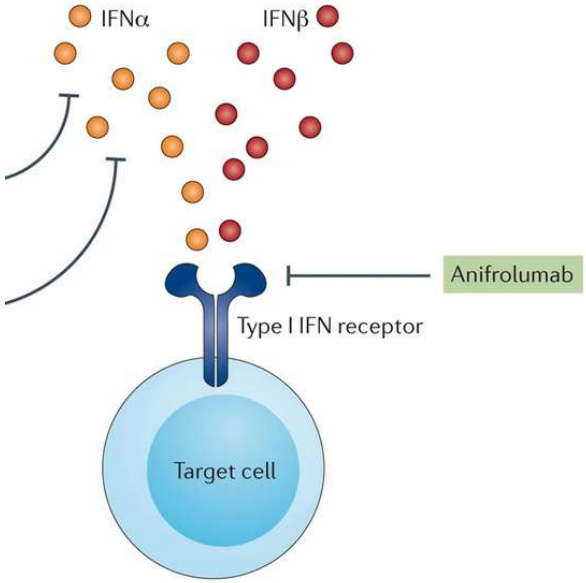
Nieuwe behandelstudies

- ANISE-II (anifrolumab)
  - Anifrolumab: type 1 interferon receptor blokker
  - Investigator-initiated trial in UMCG
  - Geïnteresseerde patiënten? -> contact met l.de.wolff01@umcg.nl
  - Inclusiecriteria: ziekteduur ≤10 jaar, ESSDAI of ESSPRI≥5, SSA positief
- NECESSITY studie
  - Hydroxychloroquine/leflunomide, hydroxychloroquine/MMF, of placebo
  - In Nederland: UMCG en UMCU



Niewold, Nat Reviews Rheumatol 2016

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BMS-986325
Bristol Myers

CD19/BCMA
CAR T-cells

Iscalimab
Novartis

Baracitinib
PUMC-Lilly

Anifrolumab
AstraZeneca

Nipocalimab
Janssen

SAR441344
Sanofi

MHV370
Novartis

Iguratomid
Jiangsu

S95011
Servier

Tofacitinib
NIDCR/PUMC

Branebrutinib
Bristol-Myers

Ianalumab
Novartis

Active clinical trials in Sjögren's

(clinicaltrials.gov)

Mechanisms of action

CD40 antigen inhibitor

Targets B-cell maturation ag

Anti-CD40 mAb

JAK1/2 inhibitor

Type 1 IFN inhib

FcRn antagonist

Anti-CD40L mAb

undisclosed

Blocks NF-kB

Anti-IL7R mAb

JAK inhibitor

BTK inhibitor

Anti-BAFF R mAb


16th International Symposium on Sjögren’s syndrome
22 april – 26 april 2024
Egmond aan zee
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