Διαχείριση ασθενών με νόσο του Still

Σπύρος Ν Νίκας

Ρευματολόγος

Ιωάννινα

Σύγκρουση συμφερόντων

Τιμητική αμοιβή από τη Sobi για την παρουσίαση

Ευχαριστώ για την τιμητική πρόσκληση

Βασικά (AOSD)

- **Σπάνιο,** αλλά **καλά** κλινικά περιγραφόμενο νόσημα

orphan disease: **επιπολασμός**

- 1 /εκ -> 1/100.000 σε Ευρώπη

orphan disease: **επίπτωση** :

- 0.16 -0.4 /100.000

- Πολύ-γονιδιακό (polygenic), συστηματικό, **αυτό-φλεγμονώδες** νόσημα

Σε αντίθεση με

- FMF (MEFV γονίδιο)
- TRAPS (TNFRS1A)

ΕΜΦΥΤΗ ανοσία (*μακροφάγα ουδετερόφιλα)*

Σε αντίθεση με την **αυτοανοσία** (*επίκτητη πχ T / B cells*)

- Σε κάθε ηλικία ενηλίκων (**νέους** όμως κυρίως) - Αναλογία φύλου: σχεδόν ίδια, λίγο πιο συχνά στις γυναίκες

Gerfaud-Valentin, M.; Jamilloux, Y.; Iwaz, J.; Sève, P. Adult-onset Still's disease. Autoimmun. Rev. 2014, 13, 708–722

Βασικά (AOSD)

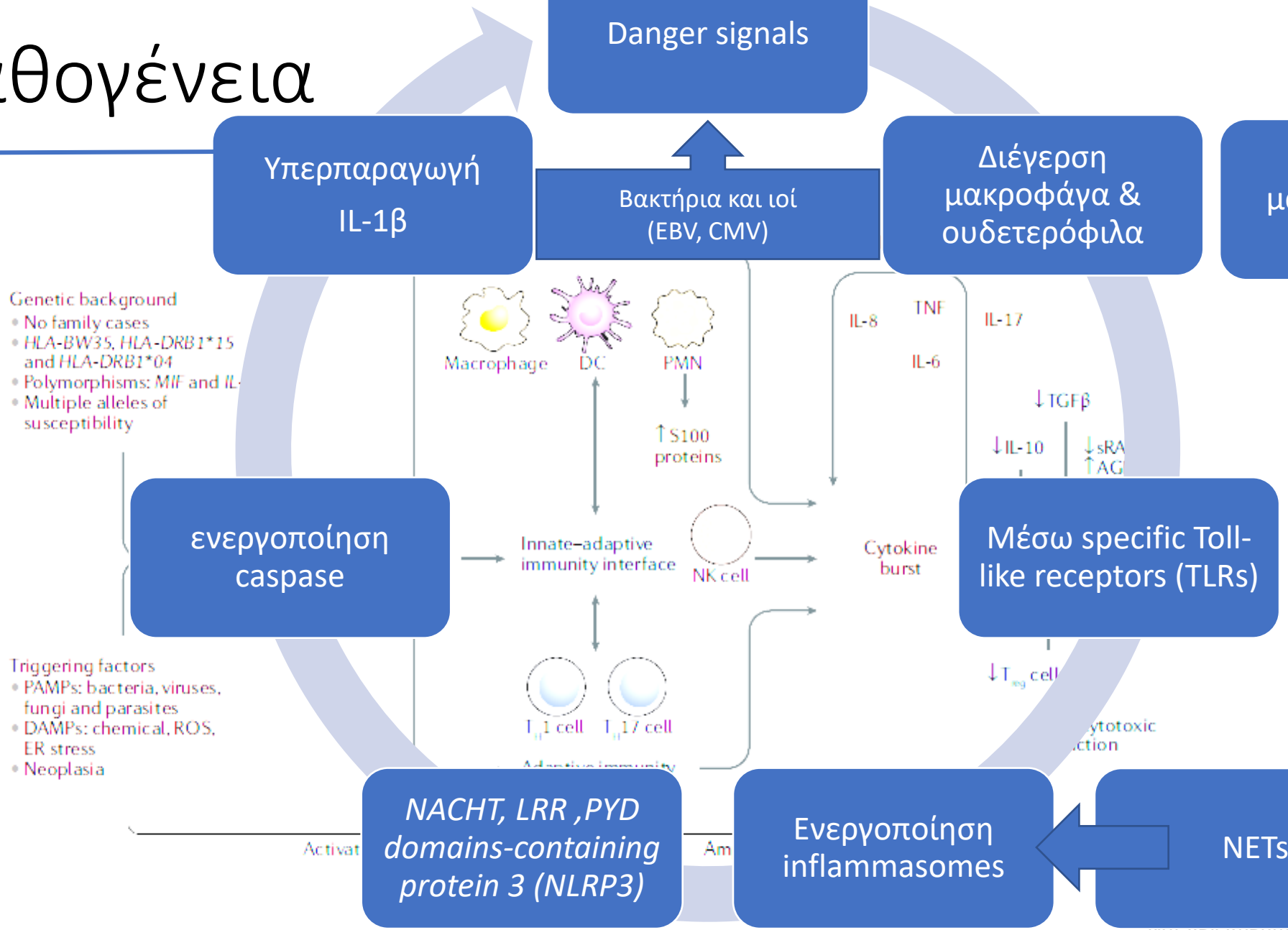
- **Έναρξη** με **έντονη φλεγμονή**, συνδυαζόμενο με ευρύ φάσμα κλινικών εκδηλώσεων & επιπλοκών
- Ο ακριβής παθογενετικός μηχανισμός είναι **άγνωστος /** *1970 (Eric Bywaters)*
- Ομοιότητες με το *systemic-onset juvenile idiopathic arthritis (1897)*

Κοινά χαρακτηριστικά
των αυτό-φλεγμονωδών νοσημάτων

- Έντονη **φλεγμονή** με *περιοδικού* χαρακτήρα **πυρετό**
- Ιστική φλεγμονή (ανάλογα με το νόσημα)
- ΕΕ: **λευκοκυττάρωση** με αυξημένα ουδετερόφιλα, ΤΚΕ, CRP
- Παθολογική δράση: *inflammasome*
- **Θεραπευτική απόκριση στην αναστολή της IL-1**

Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still's disease. Nat Rev Rheumatol. 2018 Oct;14(10):603-618.

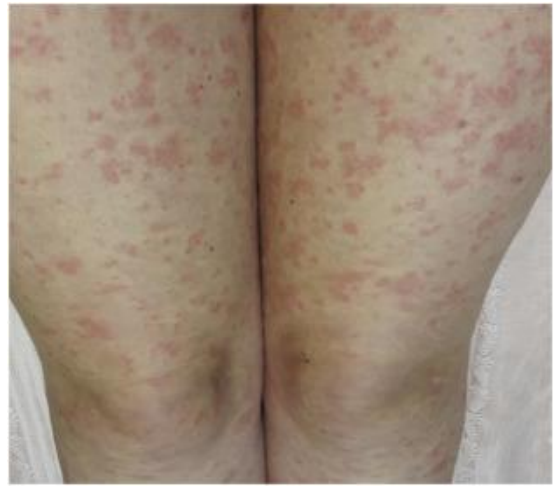
Παθογένεια



rovic S, Fautrel B..
Nat Rev Rheumatol. 2018 Oct;14(10):603-618.

Ευρήματα

Cardinal symptom



- Πυρετός

  > 39° C, 1 ή 2 (απογευματινά) spikes

- Αρθραλγίες – αρθρίτιδα

  2/3 ασθενείς, σε όλες τις αρθρώσεις (ΑΜΦ)
  -> διαβρωτική -> αγκύλωση ΠΧΚ άμφω

- Δερματικό εξάνθημα

  salmon pink: εγγύς άκρα – κορμό / πυρετό

  Πορφύρα -> επείγον -> haemophagocytic

- Λευκοκυττάρωση

- **Οδυνοφαγία**
- Μυαλγία –μυοσίτιδα (σπάνια)
- Λεμφαδενοπάθεια (συμμετρική)
- **Σπληνομεγαλία**

- **Περικαρδίτιδα**
- Μυοκαρδίτιδα
- **Πλευρίτιδα**
- Πν. νόσος
- Ηπατίτιδα

- ΤΚΕ, CRP
- Ηπατικά
- **Αυξημ φερριτίνη** (με μειωμένη γλυκοζιωμένη <20%)
- διαταραχές πηκτικότητας

Κλινική πορεία

- Μονο-κυκλική μορφή
- Πολύ-κυκλική μορφή (Υποτροπιάζουσα)
- χρόνια προοδευτική
- **Συστηματική** μορφή (φλεγμονή, οργανική βλάβη, αιματολογικές διαταραχές)
- Διαβρωτική **αρθρίτιδα**

2 φαινότυποι

GERFAUD-VALENTIN M, JAMILLOUX Y, IWAZ J, SÈVE P: Adult-onset Still's disease. Autoimmun Rev 2014; 13: 708-22.

Σοβαρές Επιπλοκές

A) secondary (acquired) haemophagocytic lymphohistiocytosis **διέγερσης μακροφάγων** (MAS)

- Συχνότητα : **10 -15%**
- Υψηλή θνησιμότητα [**40**%]
- Πιθανοί πυροδοτικοί μηχανισμοί : λοι

B) Διαταραχές πηκτικότητας :

- DIC
- thrombotic microangiopathy

	Primary HLH HLH-2004, Henter *et al.* [77]	HScore, Fardet *et al.* [78, 79]	PRINTO criteria, Ravelli *et al.* [17]
Target population	Primary HLH	Adults	sJIA
Clinical features			
Fever	+	<38.4 (0), 38.4–39.4 (33), >39.4 (49)	+
Hepatomegaly		Neither (0), either hepatomegaly or	
Splenomegaly	+	splenomegaly (23), both (38)+	
Immunosuppression		No (0), yes (18)	
Lab criteria			
Cytopaenia in more than two lineages	Either: haemoglobin <90 g/l, platelets <100 × 10^9/l, neutrophils <1 × 10^9/l	One lineage (0), two lineages (24), three lineages (34)	⩽181 × 10^9/l
Platelets			>684
Ferritin, ng/ml	⩾500	<2000 (0), 2000–6000 (35), >6000 (50)	
Hypertriglyceridaemia, mmol/L	⩾3	<1.5 (0), 1.5–4 (44), >4 (64)	>1.76
Hypofibrinogenaemia, g/l	⩽1.5	>2.5 (0), <2.5 (30)	⩽3.6
Liver function tests, IU/l		AST <30 (0), >30 (19)	AST >48
Low/absent NK cell activity	+		
Soluble CD25, U/ml	⩾2400		
Haemophagocytosis	+	No (0), yes (35)	+
Fulfillment of criteria	Molecular diagnosis consistent with primary HLH or five or more of eight criteria	Produces a probability outcome. Scores >169 are 93% sensitive and 86% specific for HLH	Febrile patient with known or suspected sJIA, ferritin >684 ng/m and two or more additional items

Score calculator (for percentage probability of secondary HLH) is available at http://saintantoine.aphp.fr/score/ [78]. PRINT
Pediatric Rheumatology International Trials Organization; HLH: haemophagocytic lymphohistiocystosis; AST: aspartate tran
minase; sJIA: systemic-onset JIA; MAS: macrophage activation syndrome.

Fardet, L.; et al Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014, 66, 2613–2620

Κριτήρια *ταξινόμησης*

Criteria	Yamaguchi et al.[71]	Fautrel et al.[40]
Major criteria	• Fever ≥39 °C lasting 1 week or more • Arthralgia lasting 2 weeks or more • Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes • Leukocytosis ≥10,000/mm^3 with neutrophil polymorphonuclear proportion ≥80%	• Spiking fever ≥39 °C • Arthralgia • Transient erythema • Pharyngitis • Neutrophil polymorphonuclear proportion ≥80% • GF proportion ≤20%
Minor criteria	• Pharyngitis or sore throat • Lymphadenopathy and/or splenomegaly • Liver enzyme abnormalities (aminotransferases) • Negative for RF or antinuclear antibodies	• Typical rash • Leukocytosis ≥10,000/mm^3
Exclusion criteria	• Absence of infection, especially sepsis and Epstein–Barr viral infection • Absence of malignant diseases, especially lymphomas • Absence of inflammatory disease, especially polyarteritis nodosa	None
Criteria requirement	At least five criteria, including two major criteria and no exclusion criteria	Four major criteria or three major criteria and two minor criteria
Classification criteria performance	• Sensitivity 96.3%, specificity 98.2%, PPV 94.6% and NPV 99.3% • Modified Yamaguchi criteria, i.e., Yamaguchi criteria and ferritin >ULN: sensitivity 100%, specificity 97.1%, PPV 87.1% and NPV 100% • Alternative modified Yamaguchi criteria, i.e., Yamaguchi criteria and GF ≤20%: sensitivity 98.2%, specificity 98.6%, PPV 93.0% and NPV 99.6%[41]	Sensitivity 87.0%, Specificity 97.8%, PPV 88.7% and NPV 97.5%[41]

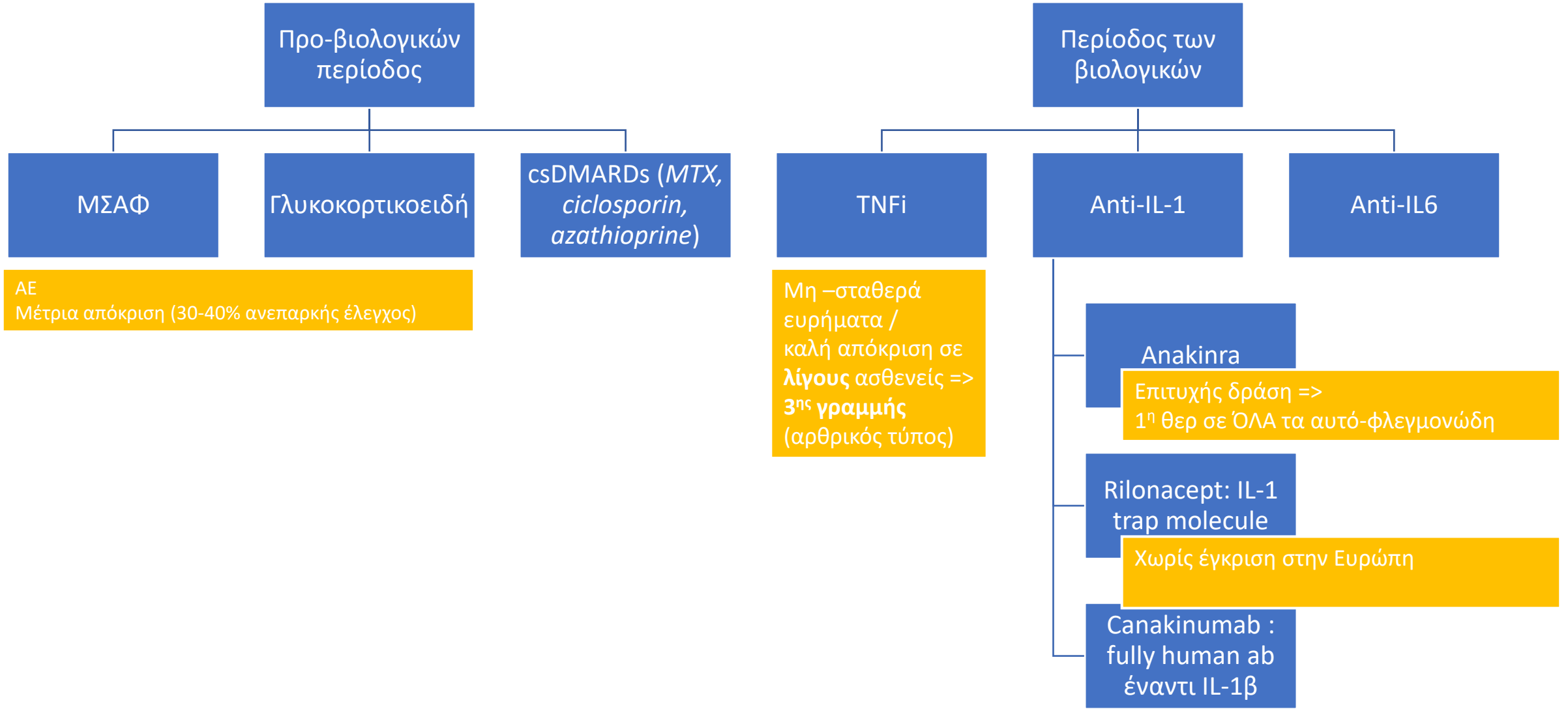
Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still's disease. Nat Rev Rheumatol. 2018 Oct;14(10):603-618

Εύκολη διάγνωση ?

	Di Benedetto P, Cipriani P, Iacono D, et al. (2020) [40]	Hu QY, Zeng T, Sun CY et al. (2019) [41]	Sfriso P, Priori R, Valesini G, et al. (2016) [35]	Gerfaud-Valentin M, Maucort-Boulch D, Hot A, et al. (2014) [42]	Fautrel B. et al. (2002) [43]	Tsai H. et al. (2012) [44]	Behrens E. D. et al. (2008) [45]
Case number	147	517	245	57	72	28	136
Nationality	Italy	China	Italy	France	France	Taiwan	United States
Female	39.5	72	47.3	53	nk	53.6	54
Average age at onset	45.2	37.7	38.8	36	35.2	8.7	5.7 Median 2
Fever $\geq$ 39 °C	100	91.3	92.6	95	84.7	100	98
Rash	74.8	79.9	67.7	77	70.8	67.9	81

Tomaras S, Goetzke CC, Kallinich T, Feist E. Adult-Onset Still's Disease: Clinical Aspects and Therapeutic Approach. J Clin Med. 2021 Feb 12;10(4):733

Αντιμετώπιση



Οδηγίες / συστάσεις
ΔΕΝ ΥΠΑΡΧΟΥΝ

Arthritis Research & Therapy

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Research article | Open Access | Published: 11 December 2019

Management of adult-onset Still's disease with interleukin-1 inhibitors: evidence- and consensus-based statements by a panel of Italian experts

Serena Colafrancesco, Maria Manara, Alessandra Bortoluzzi, Teodora Serban, Gerolamo Bianchi, Luca Cantarini, Francesco Ciccia, Lorenzo Dagna, Marcello Govoni, Carlomaurizio Montecucco, Roberta Priori, Angelo Ravelli, Paolo Sfriso, Luigi Sinigaglia & AOSD Consensus Group

Arthritis Research & Therapy **21**, Article number: 275 (2019) | Cite this article

Anakinra σε AOSD

recombinant IL-1 *receptor* antagonist

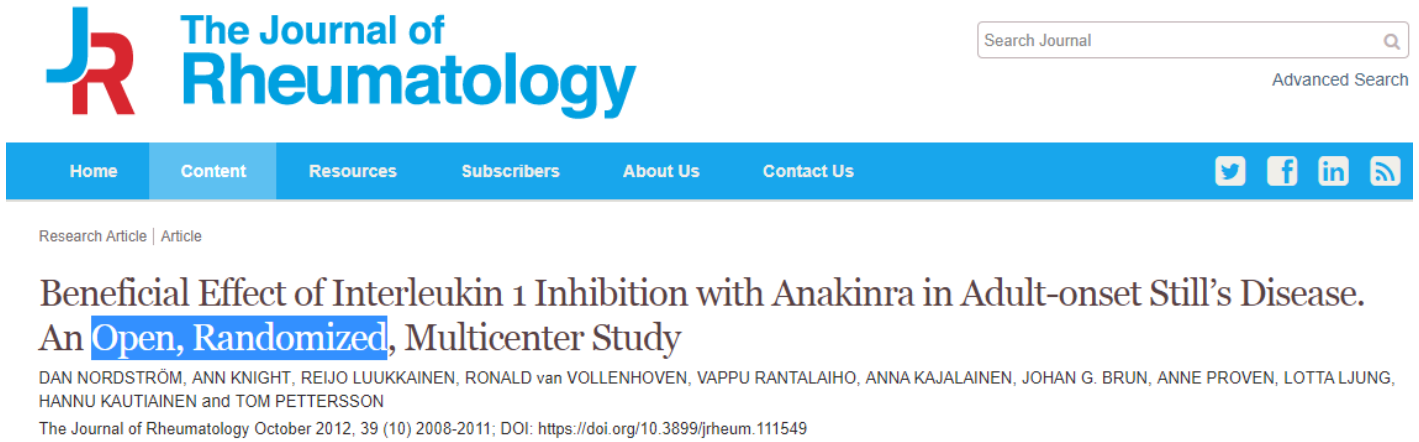
Ο 1ος βιολογικός - ευεργετική δράση σε **συστηματικά και αρθριτικά** συμπτώματα

Η απόκριση σε **συστηματικά χαρακτηριστικά είναι ταχεία**, ενώ σε αρθρώσεις απαιτείται έκθεση σε κάποιες εβδομάδες

Μείωση, ακόμη και διακοπή, της δόσης των **γλυκοκορτικοειδών** & ΜΣΑΦ

Anakinra σε AOSD

RCT



22 ασθ με ανθεκτική AOSD υπό prednisolone ≥ 10 mg/day =>

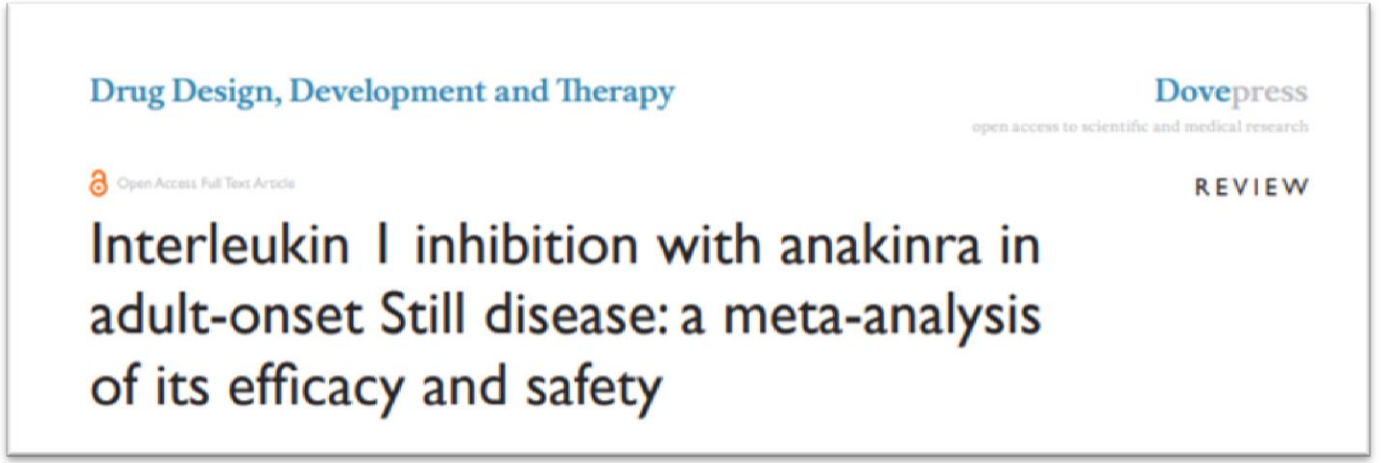
- anakinra (n = 12) ή
- DMARD (n = 10)

24 εβδ => **ΥΦΕΣΗ** :
- 6/12 ασθ υπό anakinra και
- 2/10 υπό DMARD

Nordström D, et al T. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. J Rheumatol. 2012 Oct;39(10):2008-11

Anakinra σε AOSD

μετανάλυση (i)



(*8 case series /3 εθνικά αρχεία με >100 ασθενείς με AoSD υπό anakinra*) :

- **Ύφεση (remission rate): ~ 80%** / πλήρη ύφεση στο 66.75%
- Μείωση ΓΚ σε ~ 35%

*Hong, D. et al. Interleukin 1 inhibition with anakinra in adult-onset Still disease: a meta-analysis of its efficacy and safety. Drug Des. Devel. Ther. 8, 2345–2357 (**2014**).*

Anakinra σε AOSD
μετανάλυση (ii)

Review

The treatment of adult-onset Still's disease with anakinra, a recombinant human IL-1 receptor antagonist: a systematic review of the literature

R. Giacomelli[1], J. Sota[2], P. Ruscitti[1], C. Campochiaro[3], S. Colafrancesco[4], L. Dagna[3], D. Iacono[5], F. Iannone[6], G. Lopalco[6], P. Sfriso[7], L. Cantarini[2]

(*15 άρθρα: 1 open RCT και 14 observational single-arm retrospective studies*) :

- **effectiveness** of anakinra in the treatment of patients with AOSD (~ 75%)
- largely favourable **safety** profile
- the **majority** of patients treated with anakinra may achieve a **complete remission**, also in monotherapy
- treatment with anakinra is associated with an important **CCSs-sparing effect** (~ 40%)

Giacomelli R, Sota J, et al . Clin Exp Rheumatol. ***2021*** *Jan-Feb;39(1):187-195*

Anakinra σε AOSD
(θερ. δράση)

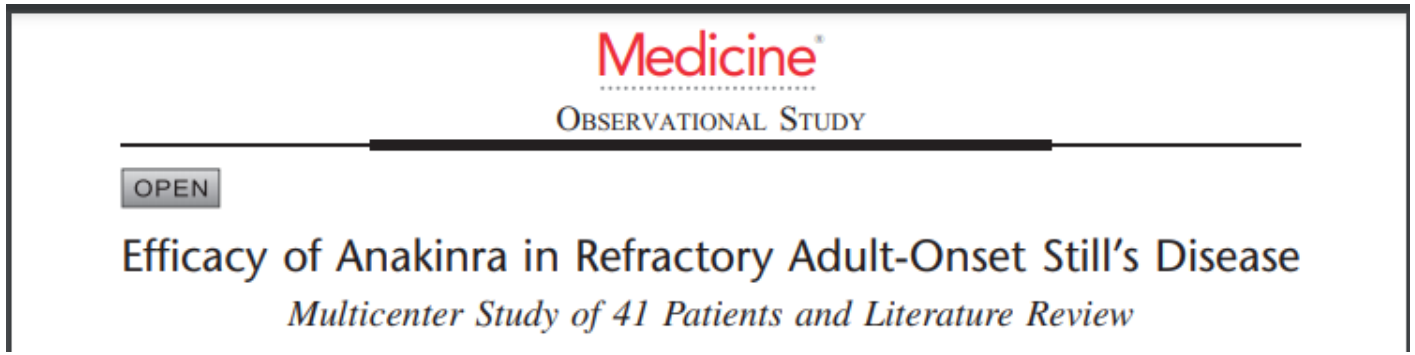
Αναδρομική **πολυκεντρική** (18 κέντρα) μελέτη παρατήρησης =>

ευεργετική δράση (3 μήνες) με βάση το Pouchot score

ανεξαρτήτως ηλικίας, φύλου, τύπου νόσου ή άλλων θερ επιλογών

Colafrancesco, S. et al. Response to interleukin-1 inhibitors in 140 Italian patients with adult-onset Still's disease: a multicentre retrospective observational study. Front. Pharmacol. 8, 369 (2017)

Anakinra σε AOSD
ταχύτητα δράσης



μείωση συχνότητας ΟΛΩΝ των κλινικών σημείων & συμπτωμάτων

με φυσιολογικές εργ τιμές στον **1 μήνα αγωγής**

με **περαιτέρω** βελτίωση > 12 μήνες =>

Μείωσης δόσης ΓΚ

F. *Ortiz-Sanjuan, R. Blanco, L. Riancho-Zarrabeitia, S. Castaneda, A. Olive, A. Riveros, et al.*
Efficacy of anakinra in refractory adult-onset Still's disease multicenter study of 41 patients and literature review Medicine, 94 (2015)

Anakinra σε AOSD

έναρξη αγωγής

Κλινικές & θεραπευτικές εκβάσεις είναι ουσιαστικά

ανεξάρτητες από το πόσο γρήγορα

θα ξεκινήσει κανείς αγωγή με anakinra

Comparison of Early vs. Delayed Anakinra Treatment in Patients With Adult Onset Still's Disease and Effect on Clinical and Laboratory Outcomes. Front Med (Lausanne). 2020 Feb 21;7:42

Anakinra σε AOSD

Ελληνικά δεδομένα

Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study

Katerina Laskari, Athanasios G Tzioufas & Haralampos M Moutsopoulos

Arthritis Research & Therapy **13**, Article number: R91 (2011) | Cite this article

84% of patients the clinical activity resolved **completely** within a **few days** (median time 0.2 months), and response was **maintained** until the last visit in *all (24) but one patient*

Laskari, K., Tzioufas, A.G. & Moutsopoulos, H.M. Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study. Arthritis Res Ther 13, R91 (2011)

Anakinra σε AOSD

ανασκόπηση

- Αγωγή με **ΟΛΟΥΣ** τους anti-IL-1 παράγοντες είναι **αποτελεσματική** στην AOSD=> **IL-1 έχει ΒΑΣΙΚΟ** ρόλο στη παθογένεια AOSD
- Τα ποσοστά πλήρους ή μερικής ύφεσης είναι **παρόμοια** από τον ένα παράγοντα στον άλλο (91–100%) και **ανώτερα** από εκβάσεις με κλασικές θεραπείες
- Ευρήματα ότι οι anti-IL-1 παράγοντες έχουν ισχυρή **steroid-sparing** δράση

Junge G, Mason J, Feist E. Adult onset Still's disease-The evidence that anti-interleukin-1 treatment is effective and well-tolerated (a comprehensive literature review). Semin Arthritis Rheum. 2017 Oct;47(2):295-302.

Και μια ματιά στην SJIA

Arthritis & Rheumatology
Vol. 71, No. 7, July 2019, pp 1163–1173
DOI 10.1002/art.40865

American College of Rheumatology
Empowering Rheumatology Professionals

Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study

- 42 ασθενείς (12 χωρίς αρθρίτιδα) – παρακολούθηση 5,8 έτη
- Διάμεσο χρονικό διάστημα μέχρι -> νόσος χωρίς ενεργότητα : **33 ημέρες**
- Στο **1 έτος** : νόσος χωρίς ενεργότητα : **76%**

Στα **5 έτη** :

- νόσος χωρίς ενεργότητα : **96%**
- Ασθενείς χωρίς αγωγή: **75%**
- υπο γλυκοκορτικοειδή: **33%**

Ter Haar, Nienke M et al. "Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study." Arthritis & rheumatology (Hoboken, N.J.) vol. 71,7 (2019): 1163-1173.

Anakinra σε AOSD

ενδείξεις

4.1 Θεραπευτικές ενδείξεις

Ρευματοειδής Αρθρίτιδα (PA)
Το Kineret ενδείκνυται για τη θεραπεία των σημείων και συμπτωμάτων της PA σε συνδυασμό με μεθοτρεξάτη, σε ενήλικες με ανεπαρκή απόκριση στη μεθοτρεξάτη όταν χρησιμοποιείται ως μονοθεραπεία.

Περιοδικά πυρετικά σύνδρομα
Το Kineret ενδείκνυται για τη θεραπεία των ακόλουθων αυτοφλεγμονωδών περιοδικών πυρετικών συνδρόμων σε ενήλικες, εφήβους, παιδιά και βρέφη ηλικίας 8 μηνών και άνω με σωματικό βάρος 10 kg και άνω:

Περιοδικά Σύνδρομα σχετιζόμενα με την Κρυοπυρίνη (CAPS)
Το Kineret ενδείκνυται για τη θεραπεία των CAPS, συμπεριλαμβανομένων των εξής:
- Πολυσυστηματική Φλεγμονώδης Νόσος Νεογνικής Έναρξης (NOMID) / Χρόνιο Παιδικό Νευρολογικό, Δερματικό, Αρθρικό Σύνδρομο (CINCA)
- Σύνδρομο Muckle-Wells (MWS)
- Οικογενές αυτοφλεγμονώδες σύνδρομο εκ ψύχους (FCAS)

Οικογενής Μεσογειακός Πυρετός (FMF)
Το Kineret ενδείκνυται για τη θεραπεία του Οικογενούς Μεσογειακού Πυρετού (FMF). Το Kineret πρέπει να χορηγείται σε συνδυασμό με κολχικίνη, εφόσον απαιτείται.

Νόσος του Still
Το Kineret ενδείκνυται για χρήση σε ενήλικες, εφήβους, παιδιά και βρέφη ηλικίας 8 μηνών και άνω με σωματικό βάρος 10 kg και άνω για τη θεραπεία της νόσου του Still, συμπεριλαμβανομένης της συστηματικής νεανικής ιδιοπαθούς αρθρίτιδας (SJIA) και της νόσου του Still των ενηλίκων (AOSD), με ενεργά συστηματικά χαρακτηριστικά μέτριας έως υψηλής δραστηριότητας της νόσου, ή σε ασθενείς με συνεχιζόμενη δραστηριότητα της νόσου μετά από θεραπεία με μη στεροειδή αντιφλεγμονώδη φάρμακα (ΜΣΑΦ) ή γλυκοκορτικοειδή.

https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information_el.pdf

Anakinra σε cytokine storm **syndromes** (IV)

** ΔΕΝ ΥΠΑΡΧΕΙ ΕΠΙΣΗΜΗ ΕΝΔΕΙΞΗ ΧΟΡΗΓΗΣΗΣ ΑΝΑΚΙΝΡΑ ΣΕ ΜΑS*

NHS England

Clinical Commissioning Policy: Anakinra/tocilizumab for the treatment of Adult-Onset Still's Disease refractory to second-line therapy (adults)

NHS England Reference: 170056P

Anakinra

Anakinra will only be commissioned for those patients who meet the following criteria:

- Patients who have failed to respond to – or are intolerant of - standard immunosuppressive therapy, including at least two of the following agents: methotrexate, cyclosporine, azathioprine, leflunomide, cyclophosphamide and mycophenolate or where standard therapies are contraindicated; AND
- Patients have been provided with information on potential adverse effects of anakinra

Response criteria for anakinra:

At least two of the following:

- Reduction of DAS28 by at least 1.2 points
- Reduction of ESR by at least 25%
- Reduction of CRP by at least 25%
- Reduction of corticosteroid dose by at least 25%

Dosing

The standard dose is 100mg/daily, but this can be increased to 200mg/daily in patients with inadequate response and also reduced to 50mg/daily in stable patients (this can be administered as 100mg on alternate days).

** Η επίσημη ένδειξη είναι 100 mg/ημ sc*

Anakinra σε AOSD

ΣΥΜΠΕΡΑΣΜΑΤΑ

AOSD : Σπάνιο νόσημα με ΕΝΤΟΝΗ φλεγμονή (**IL-1**) / **αρθρική** προσβολή

Anakinra : 1ος βιολογικός με επιτυχία στη νόσο -> στοχευμένη αγωγή (IL-1)

Ταχεία και υψηλή αποτελεσματικότητα (κυρίως στη συστηματική μορφή)

Παρόμοια αποτελεσματικότητα με άλλους παρόμοιους παράγοντες

Ικανοποιητικό προφίλ ασφάλειας

βιβλιογραφια

- AOSD : The **starting point** of the **pro-inflammatory cascade** is probably specific **danger signals** such as *pathogen-associated molecular patterns* (PAMPs) or *damage-associated molecular patterns* (DAMPs)
- Το Kineret ενδείκνυται για χρήση σε ενήλικες, εφήβους, παιδιά και βρέφη ηλικίας 8 μηνών και άνω με σωματικό βάρος 10 kg και άνω για τη θεραπεία της νόσου του Still, συμπεριλαμβανομένης της συστηματικής **νεανικής** ιδιοπαθούς αρθρίτιδας (SJIA) και της νόσου του **Still** των ενηλίκων (AOSD),
  - με **ενεργά** συστηματικά χαρακτηριστικά **μέτριας έως υψηλής** δραστηριότητας της νόσου,
  - ή σε ασθενείς με **συνεχιζόμενη** δραστηριότητα της νόσου **μετά** από θεραπεία με μη στεροειδή αντιφλεγμονώδη φάρμακα (ΜΣΑΦ) ή γλυκοκορτικοειδή.
- Το **σύνδρομο διέγερσης μακροφάγων** (MAS) είναι μια γνωστή, απειλητική για τη ζωή διαταραχή η οποία μπορεί να αναπτυχθεί σε ασθενείς με νόσο του Still.
- Το Kineret έχει συνδεθεί συχνά με την εμφάνιση **ουδετεροπενίας** (ANC < 1,5 x 109 /L) σε ελεγχόμενες με εικονικό φάρμακο μελέτες που διεξήχθησαν σε ασθενείς με ρευματοειδή αρθρίτιδα, ενώ περιπτώσεις ουδετεροπενίας έχουν παρατηρηθεί και σε ασθενείς με σύνδρομα CAPS και νόσο του Still. Γ

βιβλιογραφια

- Autoinflammation in **periodic** fever syndromes is caused by an **inborn error** of the innate immune system that results in the perturbation (διαταραχη) of pattern recognition receptors (**PRRs**), such as the *leucine-rich repeat containing family (NLR*), +> leading to an inappropriate chain reaction towards both pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns molecules **released from injured tissues** (DAMPs) =>
- In concert with this theory, genetic **errors in the NLR pathway can trigger the onset of Crohn's** disease, a very well-known disorder that was classified as an autoimmune disease until recently.

- **leukopenia** is related to an unfortunate course of disease with complications such as reactive **haemophagocytic** lymphohistiocytosis (**HLH**), (better known as **MAS**) or *thrombotic angiopathy*

- **Ferritin** contains two types of subunits: **heavy (H) and light** (L). In the bone marrow of patients with MAS, high levels of H-ferritin are found, and they correlate with disease severity

βιβλιογραφια

- Πολύ συχνές (≥1/10) τοπικές αντιδράσεις
- Το anakinra εξουδετερώνει τη βιολογική δραστικότητα της ιντερλευκίνης -1α (I**L-1α**) και της ιντερλευκίνης-1β (**IL-1β**) αναστέλλοντας ανταγωνιστικά τη δέσμευσή τους στον υποδοχέα τύπου I της ιντερλευκίνης -1 (IL-1RI).
- Many case reports describe the occurrence of **AoSD after viral** infection (with *rubella virus, measles morbillivirus, mumps virus, Epstein– Barr virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, HIV, cytomegalovirus, parvovirus B19, adenovirus, echovirus, human herpesvirus 6, influenza virus, parainfluenza viruses or coxsackie viru*s) or **bacterial** infection (with Yersinia enterocolitica
- In contrast to **monogenic**, hereditary, **periodic** fever syndromes, the underlying **genetic background of AoSD is mostly unknown**. **mutation in LACC1** (which encodes the enzyme laccase domain-containing protein 1, a multicopper oxidoreductase) has been identified in 13 patients with SoJIA from 5 consanguineous families in Saudi Arabia

Aosd

The Yamaguchi criteria, published in 1992, are the most widely used71 (Table 3); however, these criteria include **exclusion criteria** such as infections, malignancies and other rheumatic diseases. Thus, they should be used only after a broad diagnostic work-up, which is problematic in clinical practice.

The Fautrel criteria have the advantage of including **ferritin and GF** levels as diagnostic biomarkers and **do not require exclusion c**riteria

the **systemic** type includes patients mainly suffering from daily spiking fevers, typical salmon-like maculopapular rash, serositis, **hepatosplenomegaly**, and lymphadenopathy

systemic type can be distinguished into a **monocyclic and polycyclic** course

.

Aosd

A **monocyclic** (*without relapses*) course is either **self-limited** or includes **drug-free remission** that is reached over time. The initial flare with systemic manifestations and (potentially) joint involvement develops over a few weeks. Remission can be achieved with NSAIDs, steroids or other immunomodulatory agents after a few days or weeks. These treatments can be progressively tapered then stopped without relapse after **a few months**. This pattern seems to account for 19–44% of affected patients

recurrent or polycyclic course is characterized by AoSD relapses after a few months or years under immunomodulatory treatment or after its discontinuation

A **chronic and progressive course** involves continuous inflammation that is responsible for chronic and frequently **erosive** joint involvement with regular systemic flares.

- recent studies have introduced a new approach by grouping patients with AoSD into only **two** phenotypes: one with predominantly **systemic** features (higher inflammatory status and possible multi-organ damage with *haematological* complications) and one with a chronic **articular** disease course

Mas / haemophagocytic lymphohistiocytosis (HLH)

- MAS is a severe, potentially **fatal** complication of rheumatic diseases, and shares clinical and laboratory features with *primary (familial/genetic) HLH*. MAS or '**rheumatic HLH**' is classified among the **secondary** (acquired) forms of HLH occurring in the context of a rheumatic disease.5 Both the primary and secondary forms of HLH are characterized by an uncontrolled activation and *proliferation of macrophages and T lymphocytes* with *hypersecretion of pro-inflammatory* cytokines, *tissue infiltration*, **haemophagocytosis** and tissue damage. A 'cytokine storm' [of interleukin (IL)-1β, IL-2, IL-6, IL-18, IFN-γ, macrophage colonystimulating factor (MCSF), soluble TNF receptors, IL1R antagonist (IL1Ra), etc.] is suggested in a pathophysiological pathway of MAS, and treatments blocking various cytokines could be beneficial.6
- The most consistent **immunological** abnormality described in patients with primary and secondary haemophagocytic syndrome is impairment of cellular cytotoxic function with profoundly *decreased natural killer cell* activity.5 The deficient cytotoxic function may lead to **macrophage hyperactivation**. Sustained macrophage activation in AOSD may lead to reactive haemophagocytic syndrome, that is, MAS, after a sudden intensification of activation, which might be related to different triggering events.
- The prevalence varies from ***10 to 15%*** and is associated with high **mortality [40%**]. Possible triggers such as infections or medications

Mas

nine variables:

- known underlying immunosuppression
- high **temperature**
- organomegaly
- **triglyceride, ferritin**, serum aspartate **transaminase**, **Low** fibrinogen levels, **cytopenia**
- and haemophagocytosis features on bone **marrow** aspirate

Table 6. Classification criteria for MAS in SoJIA (EULAR/ACR-approved [134]).

Major criteria	• Febrile patient with (suspected) SoJIA • Serum ferritin > 684 ng/mL
Minor criteria	• Platelet count $\leq$ 181 $\times$ 109/L • Aspartate aminotransferase > 48 U/L • Triglycerides > 156 mg/dL • Fibrinogen $\leq$ 360 mg/gL
Algorithm	Both major criteria with at least two minor criteria

Anakinra

- Of note, anakinra is the only IL-1 signalling inhibitor for which **substantial long-term** results exist in terms of efficacy and safety in AoSD
- . In contrast to monogenetic autoinflammatory diseases, in AoSD, **remission can continue in some cases even after treatment is stopped**.
- However, a somewhat high withdrawal rate of 40% has been reported85 owing to loss of response over time and also to frequent injection site reactions to the required daily administrations

- https://academic.oup.com/rheumatology/article/60/6/2500/6159627 (The choice of early treatment and the impact of future relapses in adult onset Still's disease) 2021
- among all clinical variables at presentation, only initial '**intensive** treatment' and macrophage activation syndrome (**MAS**) were independently associated with an increased disease **relapse** rate with an odds ratio of 6.848 and 4.020, respectively

- Relevant **safety considerations for all IL-1** antagonists include **infections** and the risk of **macrophage activation syndrome**. Whether macrophage activation syndrome should be considered a characteristic systemic manifestation of SoJIA and AoSD, or whether in some instances it is at least an adverse paradoxical effect of IL-1 inhibition, is **unknown102**

- The 3 anti-IL-1 agents reviewed show **no clear evidence for differences in initial efficacy**, but **later losses in efficacy with anakinra** are thought to reflect low drug levels,

- **tolerability for anakinra is less** than that for rilonacept and canakinumab. The lesser tolerability for anakinra, is often related to frequent **injection site reactions**.

- canakinumab, as a **fully** human antibody, causes little to **no injection site reactions** or immunogenicity

IL6

- For the two different IL-6 **receptor antagonists** (tocilizumab and sarilumab) currently available in daily practice for treating rheumatic diseases, **only case series for tocilizumab in AoSD** have been published and reported at conferences104

- observed anti-inflammatory effects were strong, rapid and sustained for most of these patients. tocilizumab, it was reported that **joint manifestations seem to be more refractory** to treatment than systemic manifestations108

- A **meta-analysis** of 10 original studies (147 individuals) on the efficacy of tocilizumab and AoSD showed overall high **partial and complete remission rates of 85% and 77%,** respectively

- Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, showed promising results in the treatment of AoSD in a pilot study. **Both the systemic features and the arthritic** manifestations improved [101–103]. A 2018 meta-analysis investigated the benefits of tocilizumab in patients with AoSD and definitely showed signals of efficacy compared to conventional therapy regimes and was well acceptable in terms of safety [104]. The other IL-6 receptor antagonist, sarilumab, was reported to be effective as a steroidsparing agent [105

Canacinumab

The other strategy for inhibiting IL-1 that has been intensively studied to date consists of a fully human antibody against IL-1β, canakinumab [93–95]. Canakinumab is currently licensed for AoSD, SoJIA, periodic fever syndromes and gout [96]. The CONSIDER study (Canakinumab for Treatment of Adult-Onset Still's Disease to Achieve Reduction of Arthritic Manifestation), a phase II, randomized, double-blind, placebo-controlled, multicentre, investigator-initiated trial was terminated prematurely and did not reach the primary outcome (ΔDAS28 > 1.2). However, this trial demonstrated that in AoSD, treatment with canakinumab yielded improvement in several clinical aspects of the disease, while showing a favourable safety profile [97–99].

Canacinumab

- **Ilaris is a medicine for treating the following inflammatory conditions:**

- **4 types of periodic fever syndromes (diseases marked by recurring inflammation and fever) in adults and children aged 2 and above:**
  - **cryopyrin-associated periodic syndromes (CAPS); (3)**
  - **tumour necrosis factor receptor associated periodic syndrome (TRAPS);**
  - **hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD);**
  - **familial mediterranean fever (FMF)**
- **Still's disease, a rare disease causing inflammation of joints as well as rash and fever (in adults and children aged 2 and above);**
- **Gouty arthritis, painful inflammation of the joints caused by deposit of urate crystals (in adults).**

Because of the similarities between childhood Still's disease and the adult form (adult-onset Still's disease, AOSD), **Ilaris is expected to have similar benefits in adults.**

Caps

- FCAS : το πιο **ηπιο** urticaria, arthralgia, and **fever** after general exposure to **cold**
- MWS is FVAS + characterized by renal amyloidosis, sensorineural **hearing** loss, and **conjunctivitis**
- The most **severe** is **NOMID** The hallmark of NOMID is neonatal onset of cutaneous symptoms along with end-organ damage. These include the “triad” of **arthropathy**, chronic urticaria, and **central nervous system** (aseptic meningitis and mental retardation)

- Familial Mediterranean fever (**FMF**) is an inherited autoinflammatory disease characterized by recurrent episodes (attacks) of **fever** and acute inflammation of the membranes lining the **abdomen, joints, and lungs**. In some cases, affected individuals may develop **skin** rashes (erysipelas like erythema) affecting the lower legs.

TRAPS

- periodic episodes or attacks of **fever** associated with additional symptoms including muscle pain (myalgia), abdominal pain, headaches and **skin rashes.** The specific symptoms can vary greatly from one person to another. The duration of the characteristic episodes can also vary, lasting anywhere from a couple days to one week to more than one month. Onset is usually during infancy or childhood. TRAPS is caused by **mutations** of the tumor necrosis factor **receptor-1** (T**NFRSF1A**) gene that encodes the 55-kDa receptor for TNF.

- **Febrile episodes typically associated with lymphadenopathy, abdominal pain, and an elevated serum polyclonal immunoglobulin D (IgD) level**

Rilonacept

- θεραπεία περιοδικών συνδρόμων που σχετίζονται με την **κρυοπυρίνη** (CAPS). Τα CAPS αποτελούν ομάδα ασθενειών στις οποίες οι ασθενείς παρουσιάζουν ελάττωμα στο **γονίδιο** που παράγει μία πρωτεΐνη που ονομάζεται **κρυοπυρίνη**. Αυτό προκαλεί φλεγμονή σε πολλά σημεία του σώματος, με συμπτώματα όπως **πυρετός, εξάνθημα, πόνος στις αρθρώσεις** και κόπωση. Επίσης, ενδέχεται να προκύψουν και σοβαρής μορφής αναπηρίες, όπως **κώφωση και απώλεια της όρασης**.
- Το Rilonacept Regeneron χορηγείται για τη θεραπεία των CAPS που προκαλούν σοβαρής μορφής συμπτώματα σε ενήλικες και παιδιά ηλικίας 12 ετών και άνω, συμπερι λαμβανομένου του οικογενούς αυτοφλεγμονώδους συνδρόμου εκ ψύχους **και του συνδρόμου Muckle-Wells (MWSFCAS)** ().
- Καθώς προσκολλάται στην **ιντερλευκίνη-1 βήτα**, η **rilonacept** αναστέλλει τη δράσης της, συμβάλλοντας στην ανακούφιση από τα συμπτώματα της ασθένειας.

Rilonacept (FDA)

- ARCALYST® (rilonacept) is an interleukin-1 blocker indicated for:

- Treatment of recurrent **pericarditis** (RP) and reduction in risk of recurrence in adults and children 12 years and older.
- Treatment of Cryopyrin-Associated Periodic Syndromes (**CAPS**), including Familial Cold Auto-inflammatory Syndrome (FCAS), and Muckle-Wells Syndrome (MWS) in adults and children 12 years and older.
- Maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing 10 kg or more.

- The marketing authorisation **holder** (MAH) responsible for Rilonacept Regeneron was Regeneron UK Limited.
- The European Commission was notified by letter dated 20 September **2012** of the MAH's decision to **voluntarily withdraw** the marketing authorisation for Rilonacept Regeneron for commercial reasons.
- The product had **never been placed on the market** in any country of the European Community.

Autoinflammatory Diseases 'Not So Rare After All,' Expert Says

- https://www.medscape.com/viewarticle/955315?src=soc_fb_210726_mscpedt_news_mdscp_autoinflammatory#vp_2

SAIDs

- Systemic autoinflammatory diseases () are a growing group of disorders caused by a dysregulation of the innate immune system leading to episodes of systemic inflammation. In **1997, MEFV** was the first **gene** identified as disease causing for *Familial Mediterranean Fever*, the **most common hereditary** SAID. In most cases, **autoinflammatory diseases have a strong genetic background with mutations in single genes**. Since 1997 more than **30 new genes** associated with autoinflammatory diseases have been identified, affecting different parts of the innate immune system.
- Nevertheless, for at least **40-60% of patients with phenotypes typical for SAIDs, a distinct diagnosis cannot** be met, leading to undefined SAIDs (uSAIDs). However, SAIDs can also be of **polygenic or multifactorial** origin, with environmental influence modulating the phenotype.. Diagnosis is often based on clinical presentation and genetic testing. The **timeline from onset to diagnosis takes up to 7.3 years**, highlighting the indisputable need to identify new treatment and diagnostic targets.

Overview of the most common hereditary monogenic SAIDs. Abbreviations: AR: autosomal recessive; AD: autosomal dominant.

Disease		OMIM	Affected Gene	location	reported INFEVERS variants	Inheritance	Prevalence	Male/female ratio	Treatment	Mechanism
FMF		#249100	MEFV	16pl3.3	365	AR	• Turkey 1:4000-1:1000 [74] • Israel 1:1000 (in non-Ashkenazi Jews) • Armenia 1:500 [38]	1:1 [75]	• Colchicine • IL-1 inhibition	Inflammasomopathy
NLRP3-AID	*FCAS* *MWS* *NOMID*	#120100 #191900 #607115	NLRP3	lq44	227	AD	France 1:360000 [76]	2:1 [77] 1:1 [77] 1:1 [77]	• IL-1 inhibition • IL-1 blockage • NSAIDs/Corticosteroids (primary maintenance therapy)	Inflammasomopathy
MKD		#260920	MVK	12q24.11	227	AR	Netherlands 5:1000000 [78]	1:1 [79]	• IL-1 blockage • IL-6 blockage • TNF-α blockage • NSAIDs/glucocorticoids (symptom relief during inflammation) • Etanercept	Inflammasomopathy
TRAPS		#142680	TNFRS1A	12pl3.31	163	AD	1:1000000 [68]	3:2 [66]	• IL-1 blockage • Etanerecept • NSAIDs/Corticosteroids (primary maintenance therapy)	protein folding disorder

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7610735/

Εκκρεμότητες

- Ποσο συχνα είναι τα συμπτωματα το καθενα