«Αντι-IL-1 θεραπεία 20 χρόνια μετά»
Η αναστολή της IL-1 σε ένα ευρύ φάσμα νοσημάτων

424 ΓΣΝΕ
ΤΜΗΜΑ ΛΟΙΜΩΞΕΩΝ

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Διευθυντής Τμήματος Λοιμώξεων και Βιοπροστασίας 424 ΓΣΝΕ

ΔΙΑΛΕΞΗ 02/10/2022

ΔΗΛΩΣΗ ΣΥΓΚΡΟΥΣΗΣ ΣΥΜΦΕΡΟΝΤΩΝ

Συμμετοχή σε advisory boards και ως προσκεκλημένος ομιλητής
Angellini
Pfizer

Για την παρούσα ομιλία έχω λάβει τιμητική αμοιβή από την εταιρεία SOBI

ΕΙΣΑΓΩΓΗ -ΠΕΡΙΓΡΑΜΜΑ

Η αναστολή της IL-1 σε ένα **ευρύ φάσμα** νοσημάτων……

Ρόλος IL-1 παραγωγή –σηματοδότηση

Νοσήματα που έχει επίσημη ένδειξη

Νοσήματα που έχει χρησιμοποιηθεί με αποτελέσματα

Νοσήματα που δυνητικά μπορεί να χρησιμοποιηθεί

ΕΙΣΑΓΩΓΗ-ΠΕΡΙΓΡΑΜΜΑ

Η ιντερλευκίνη (IL)-1, περιγράφηκε για πρώτη φορά πριν από περίπου 35 χρόνια ως εκκρινόμενο προϊόν των μονοκυττάρων και των ουδετερόφιλων

Αφορά κυρίως στις **IL-1α** και **IL-1β**, δύο βασικές κυτταροκίνες στην ενεργοποίηση της **μη-ειδικής ή εγγενούς ανοσίας.**

Αυτές οι κυτταροκίνες ήταν από τις πρώτες πρωτεΐνες που ταυτοποιήθηκαν ως ενορχηστρωτές της επικοινωνίας των λευκοκυττάρων, δημιουργώντας την κατηγορία των εκκρινόμενων προϊόντων που σήμερα είναι γνωστές ως ιντερλευκίνες

Τα **μονοκύτταρα**, τα **μακροφάγα** και τα **δενδριτικά** κύτταρα, καθώς και τα **ουδετερόφιλα**, συγκαταλέγονται στα κύτταρα του ανοσοποιητικού συστήματος που είναι ικανά να παράγουν μεγάλες ποσότητες IL-1β.

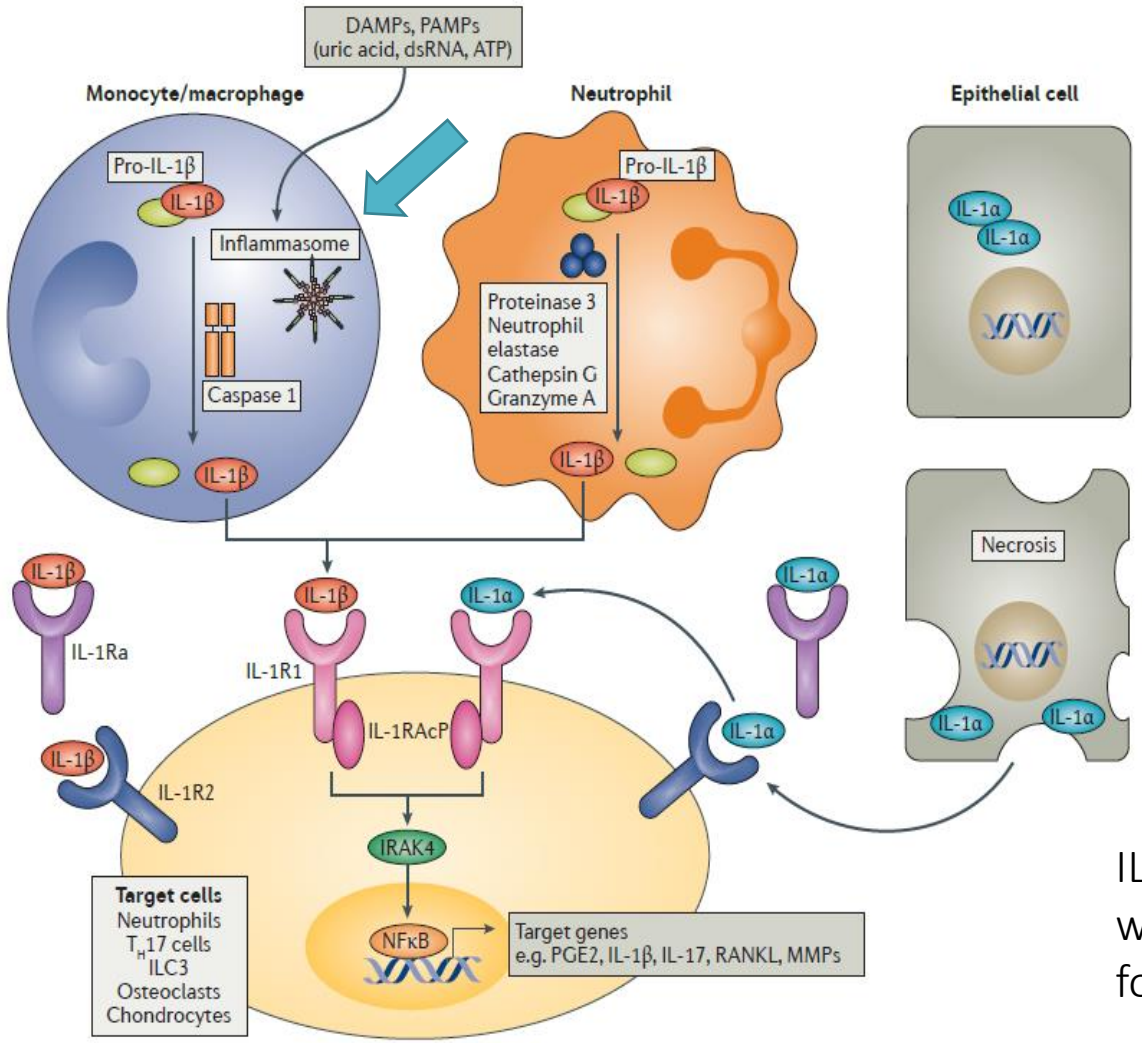
Η βιολογικά ενεργή μορφή της **IL-1β** είναι ένα μόριο μεγέθους 17 kD που προκύπτει από την ενδοκυττάρια επεξεργασία μιας βιολογικά ανενεργής πρόδρομης ουσίας μεγέθους 31 kD (**pro-IL-1β**)

Η IL-1 α βρίσκεται στα επιθηλιακά και ενδοθηλιακά κύτταρα

Η ενεργοποίηση της IL-1β επιτελείται συνήθως ως μια διαδικασία δύο σταδίων. Αρχικά, επάγεται η μεταγραφή του mRNA της IL-1β και μεταφράζεται ως η πρόδρομη πρωτεΐνη IL-1β (pro- IL-1β). Το δεύτερο βήμα βασίζεται στη δράση ενδοκυτταρικών ενζύμων (κασπάση μονοκυττάρων-μακροφάγων, πρωτεϊνάσες ουδετεροφίλων), τα οποία διασπούν την pro-IL-1β στο βιολογικά ενεργό μόριο των 17kD. Η ώριμη IL-1β εκκρίνεται στη συνέχεια, προσδένεται **στον υποδοχέα της IL-1** και ασκεί τη βιολογική της δράση.

Schett, G. et al.(2015) Nat. Rev. Rheumatol.

IL-1 ΠΑΡΑΓΩΓΗ ΚΑΙ ΣΗΜΑΤΟΔΟΤΗΣΗ



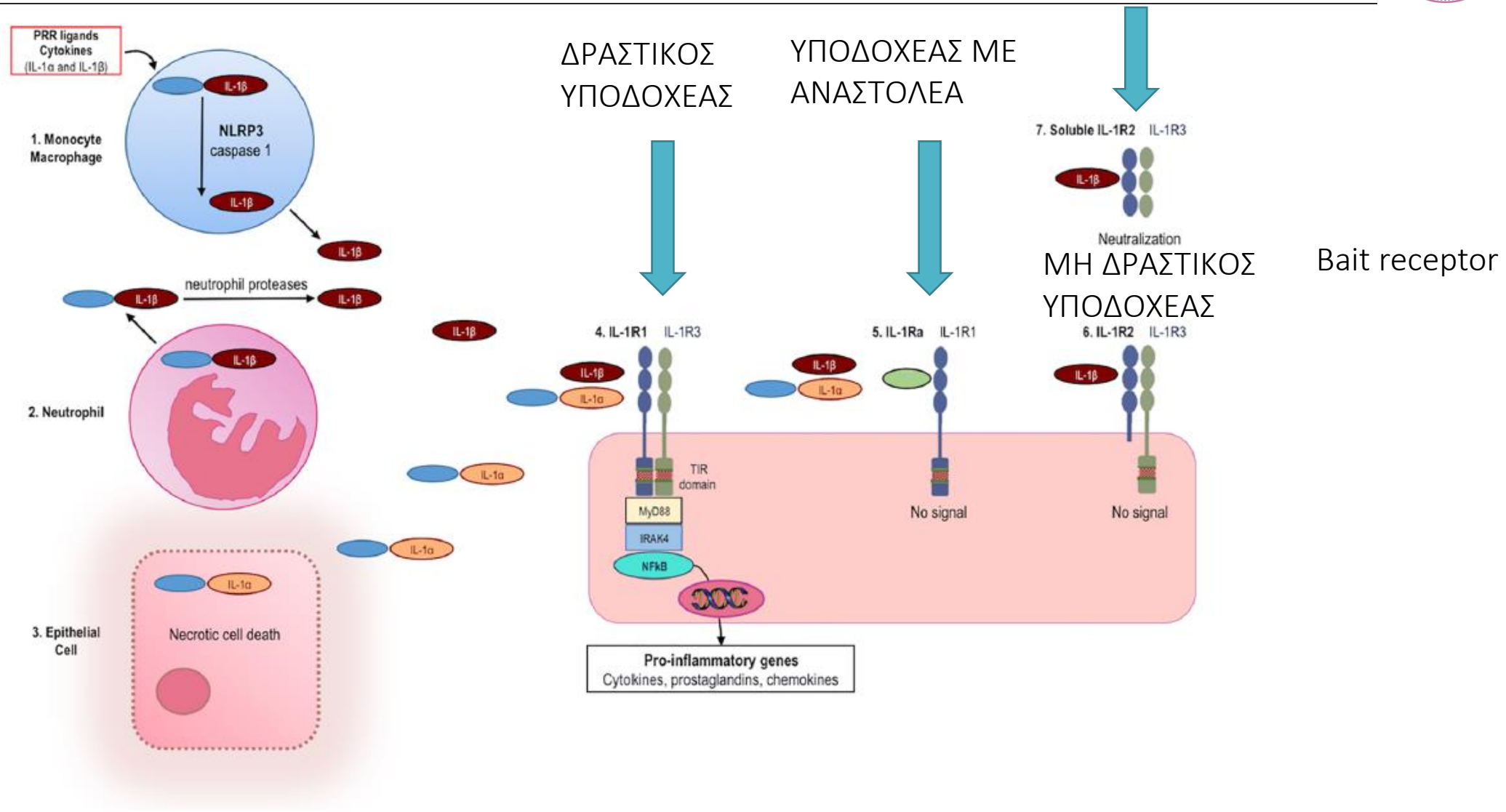
Key points

- The interleukin (IL)-1 family has 11 members, including the proinflammatory proteins IL-1α and IL-1β, as well the anti-inflammatory IL-1 receptor antagonist
- Active IL-1β is produced by cleavage of pro-IL-1β by inflammasome-mediated caspase-1 or neutrophil proteases
- IL-1α is produced and accumulated in the cell and is released upon cell necrosis, thereby serving as an 'alarmin'
- In addition to mediating acute inflammatory responses, IL-1α and IL-1β link innate and adaptive immunity, facilitating the differentiation of IL-17-producing T cells and innate immune cells
- Therapeutic inhibition of IL-1 is highly effective in rare autoinflammatory syndromes, but also in more prevalent diseases involving the inflammasome and neutrophil activation such as crystal-induced arthropathies

IL-1a is constitutively present in endothelial and epithelial cells, whereas IL-1b is inducible in myeloid cells and released following cleavage by caspase-1

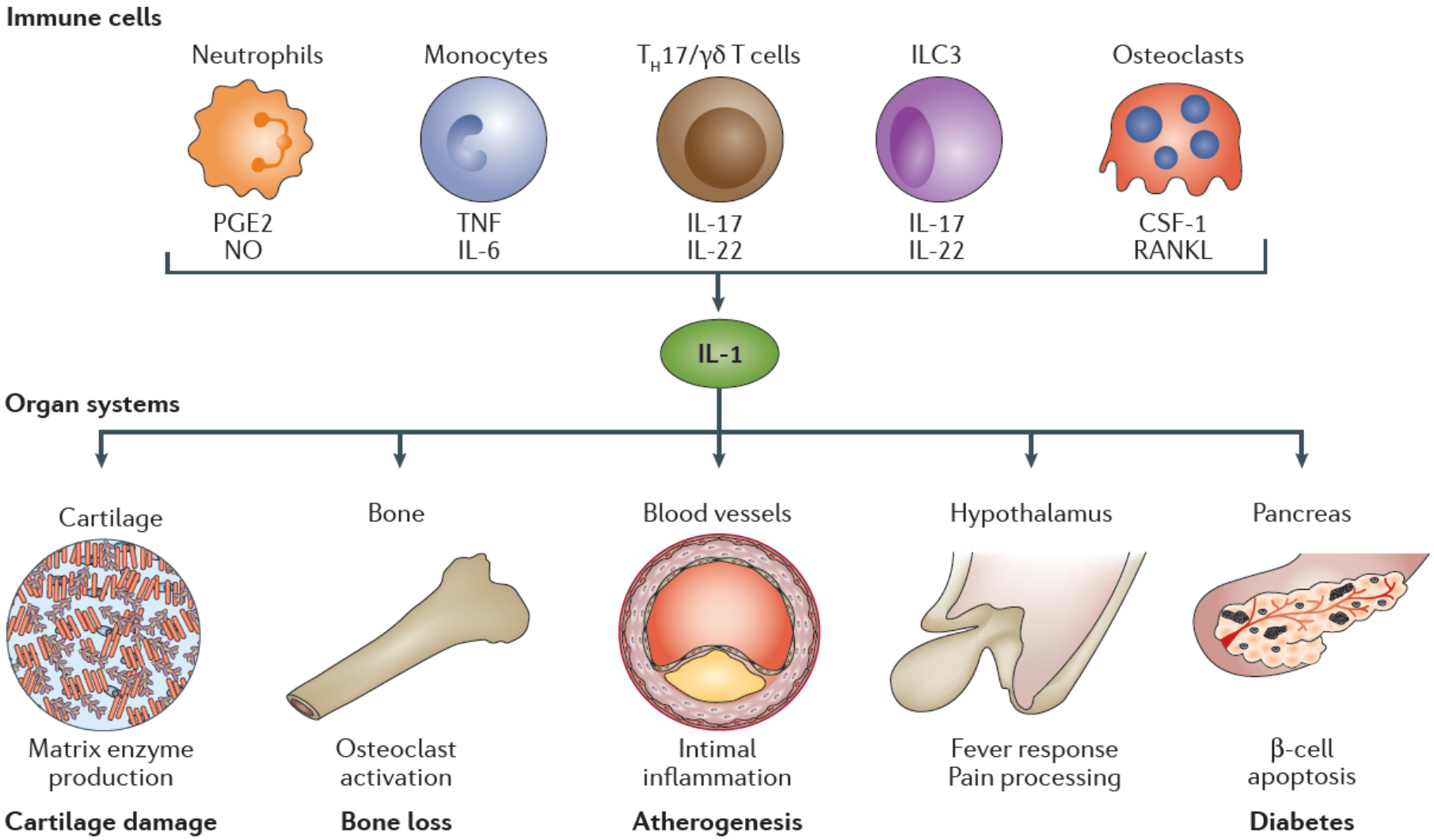
Schett, G. et al.(2015) Nat. Rev. Rheumatol.
Cavalli G and Dinarello CA (2018) Front. Pharmacol. 9:1157

Η ΑΝΑΣΤΟΛΗ ΤΗΣ ΔΡΑΣΗΣ ΤΗΣ IL-1



Cavalli G and Dinarello CA (2018) Anakinra Therapy for Non-cancer Inflammatory Diseases.Front. Pharmacol. 9:1157

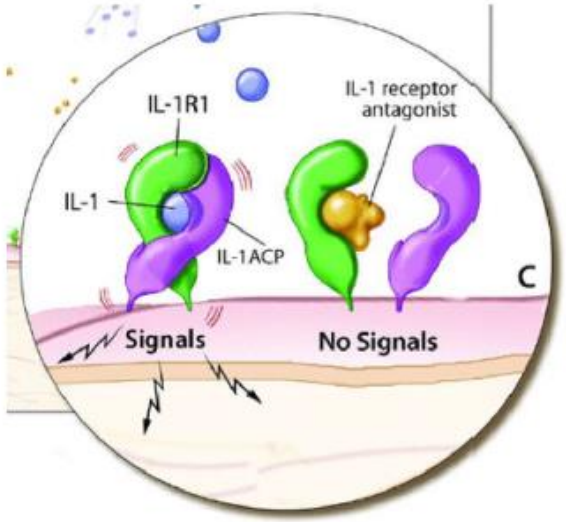
ΠΛΕΙΟΤΡΟΠΙΚΕΣ ΔΡΑΣΕΙΣ IL-1

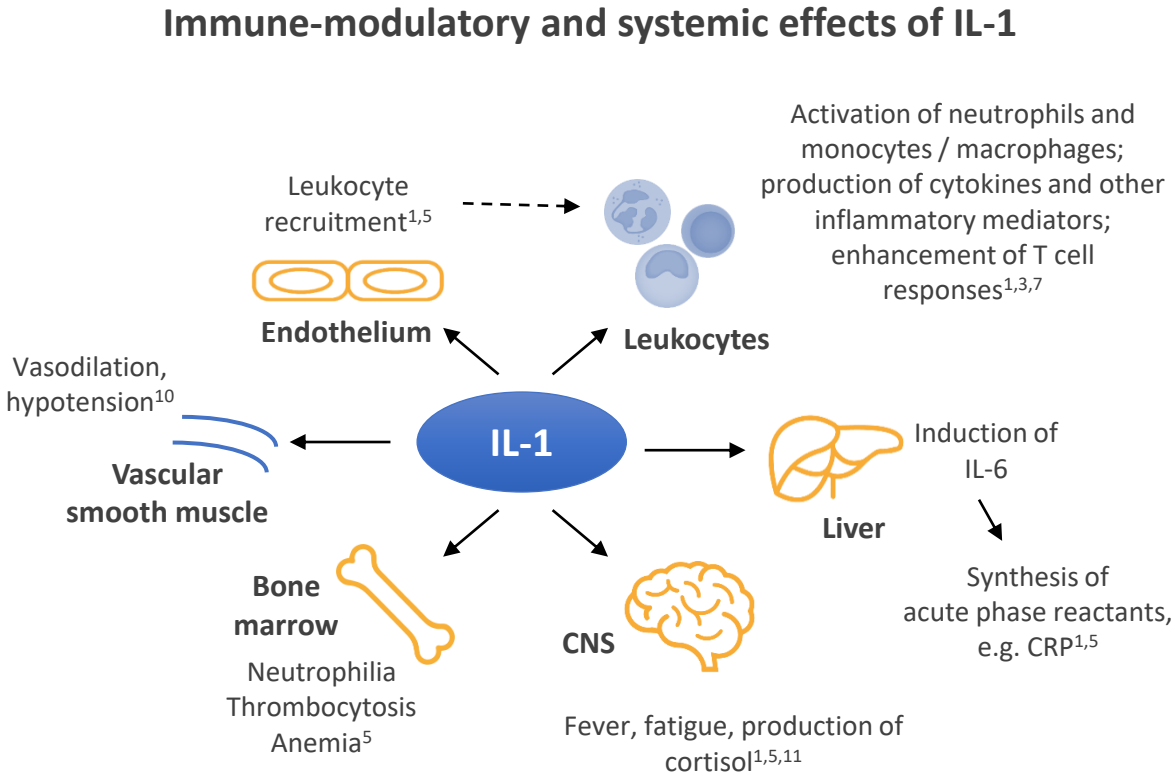


Schett, G. et al.(2015) Nat. Rev. Rheumatol.

ΣΥΜΠΡΑΞΗ ΚΑΙ ΑΝΑΣΤΟΛΗ

anakinra, the recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra);
IL-1Ra prevents the binding of IL-1a as well as IL-1b to IL-1R1





Cavalli G and Dinarello CA (2018) Front. Pharmacol. 9:1157

Chung, Juyeon, "Reducing Mortality from Septic Shock Using an Interleukin-1 Receptor Antagonist" (2017). Yale School of Medicine Physician Associate Program Theses. 41.

ΦΛΕΓΜΟΝΩΔΕΙΣ ΔΙΕΡΓΑΣΙΕΣ ΜΕ ΔΙΑΜΕΣΟΛΑΒΗΣΗ IL-1

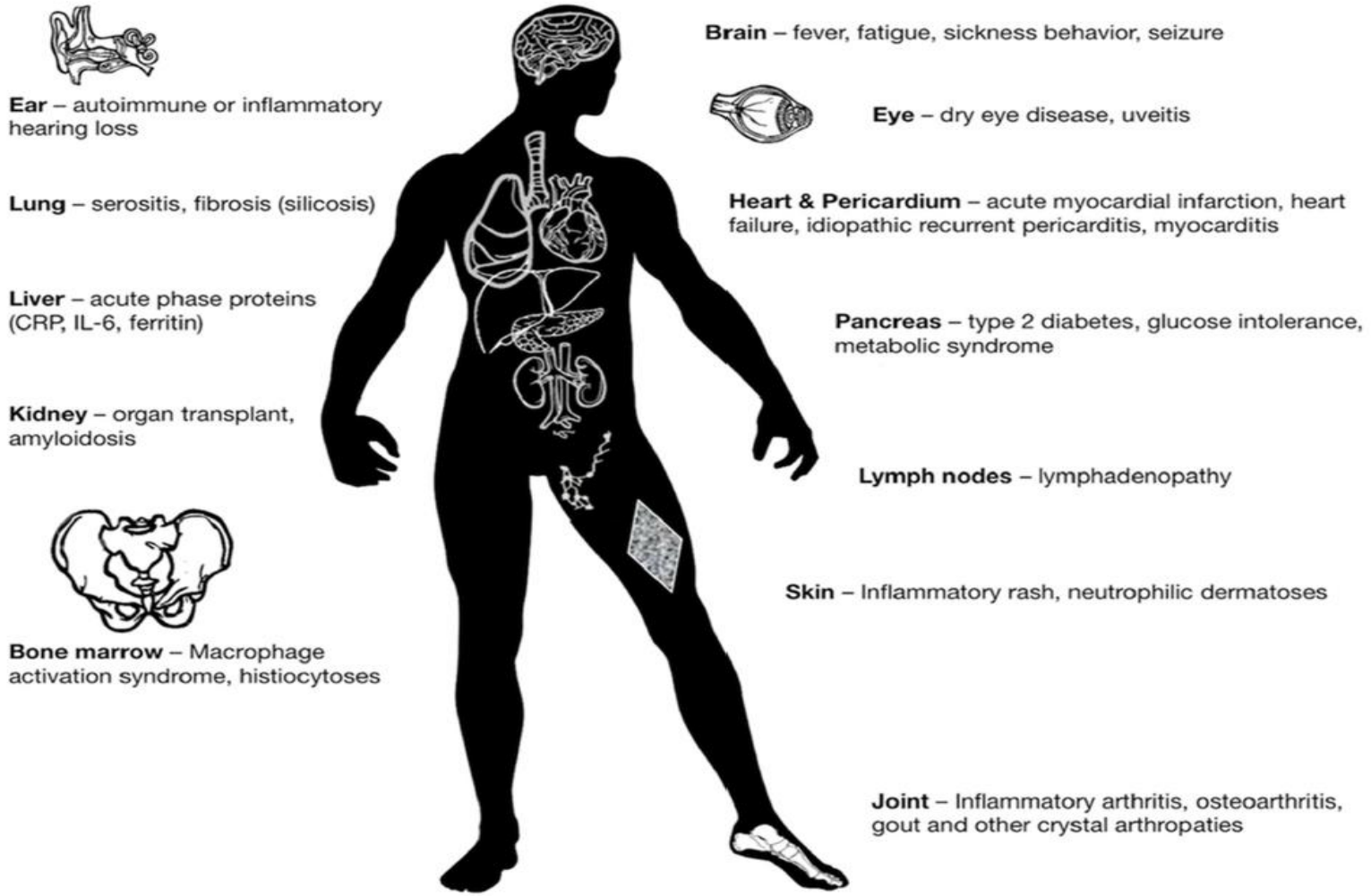
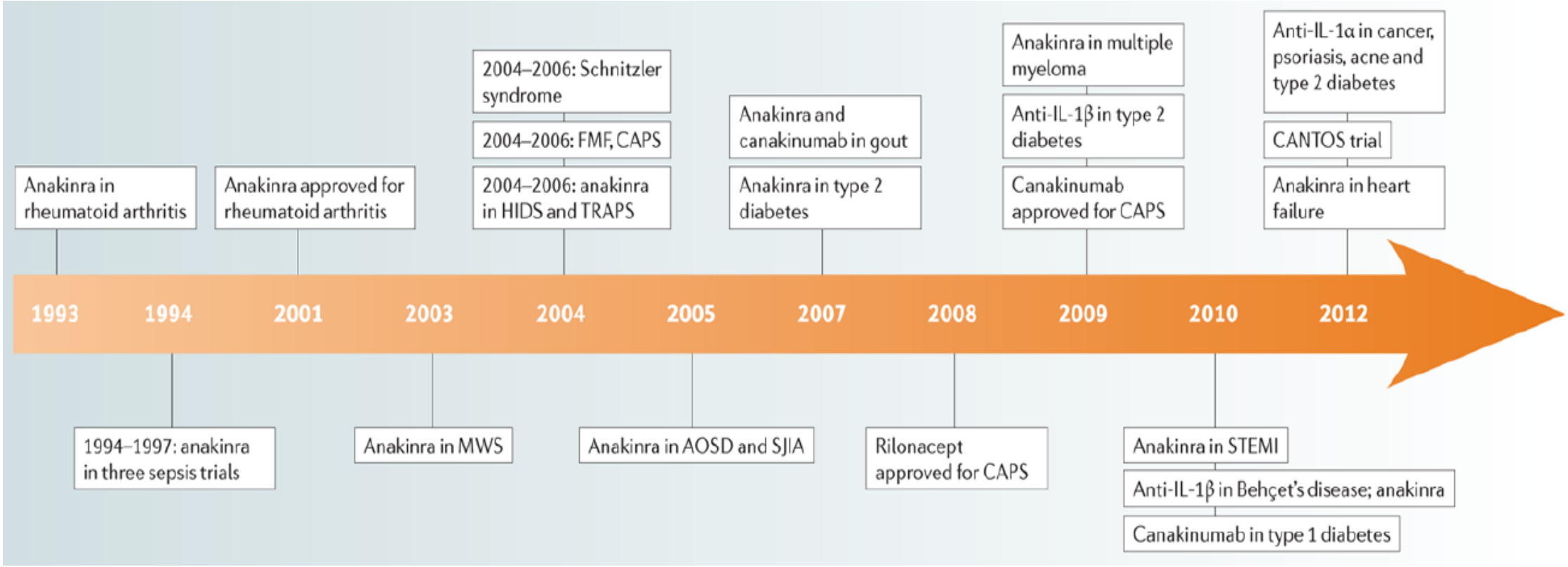


FIGURE 2 | Clinical manifestations of IL-1-mediated inflammation, which are reversible upon treatment with anakinra.

Cavalli G and Dinarello CA (2018) Anakinra Therapy for Non-cancer Inflammatory Diseases.Front. Pharmacol. 9:1157

IL-1-blocking agents in various disease states



Dinarello, Nat Rev Drug Discov. 2012 August ; 11(8): 633–652

4

ισχυροί αναστολείς της IL-1

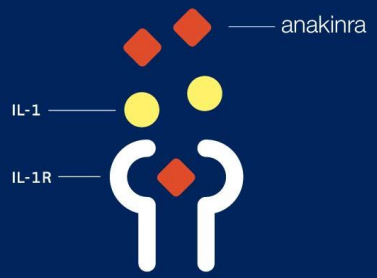
διαθέσιμοι για κλινική χρήση ή σε προχωρημένο στάδιο κλινικής ανάπτυξης

anakinra

canakinumab

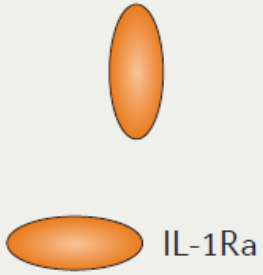
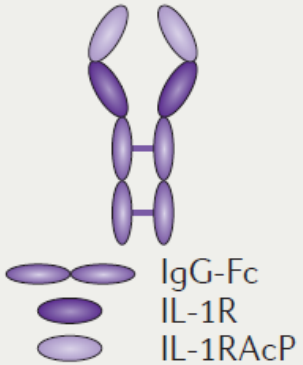
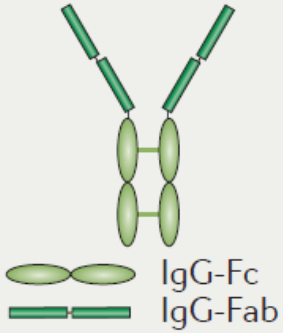
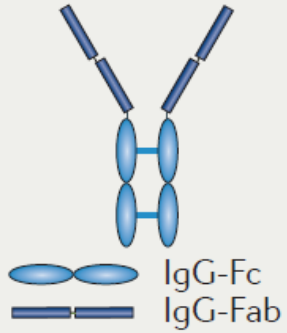
rilonacept

gevokizumab



οι οποίοι όχι μόνο αποτελούν αποτελεσματικές θεραπείες, αλλά συνέβαλαν επίσης στη βελτίωση της κατανόησης του ρόλου της IL-1 στις ανθρώπινες νόσους *(Schett).*

ΠΑΡΑΓΟΝΤΕΣ ΠΟΥ ΣΤΟΧΕΥΟΥΝ ΤΟ ΔΡΟΜΟ ΤΗΣ IL-1

	Anakinra	Rilonacept	Canakinumab	Gevokizumab
				
Parameter	**IL-1Ra**	**IL-1R/IL-1RAcP-Fc**	**Anti-IL-1β antibody**	**Anti-IL-1β antibody**
Structure Binding to IL-1α Affinity to IL-1β Half life Dose	Recombinant protein Yes None 5 hours 100 mg daily	Fc fusion protein Yes 0.5 pmol 8 days 160 mg/week	IgG1 mAb No 23 pmol 26 days 4 mg/kg/4–8 weeks 150 mg single dose	IgG2 mAb No 300 fmol 22 days –
Approved Off label use	RA, CAPS sJIA, AOSD, CPPD Gout, CPPD, HACD Schnitzler syndrome	CAPS (only USA) –	CAPS, gout, sJIA AOSD, Schnitzler syndrome	– –
In testing	–	–	CVD, diabetes	CVD, diabetes, Behçet syndrome, pyoderma gangrenosum

Schett, G. et al.(2015) Nat. Rev. Rheumatol.

ΧΡΗΣΗ ΤΟΥ ANAKINRA

TABLE 1 | Anakinra for hereditary systemic inflammatory diseases.

Familial Mediterranean fever (FMF; Meinzer et al., 2011; Ozen et al., 2011)
CAPS (Hawkins et al., 2003; Goldbach-Mansky et al., 2006; Kullenberg et al., 2016)
TRAPS (Simon et al., 2004; Gattorno et al., 2008a)
PAPA (Dierselhuis et al., 2005; Brenner et al., 2009; Braun-Falco et al., 2011; Schellevis et al., 2011)
PASH (Braun-Falco et al., 2011; Marzano et al., 2013)
DIRA (Aksentijevich et al., 2009; Reddy et al., 2009; Sakran et al., 2013)
Blau syndrome/granulomatous arthritis (Arostegui et al., 2007; Punzi et al., 2011)
Mevalonate kinase deficiency/hyper-IgD syndrome (Ruiz Gomez et al., 2012)
Majeed syndrome (Herlin et al., 2013)
NLRP12 autoinflammatory syndrome (Jeru, 2011)

TABLE 2 | Anakinra for systemic and local inflammatory diseases.

Schnitzler syndrome (Ryan et al., 2008)
Behçet disease (Cantarini et al., 2015b)
Secondary amyloidosis (Moser et al., 2009; Ait-Abdesselam et al., 2011; Stankovic Stojanovic et al., 2012)
Henoch–Schonlein purpura (Boyer et al., 2011)
Idiopathic recurrent pericarditis (Picco et al., 2009; Brucato et al., 2016)
Systemic-onset juvenile idiopathic arthritis (Gattorno et al., 2008b; Vastert et al., 2014)
Adult-onset still disease (Fitzgerald et al., 2005; Cavalli et al., 2015b; Colafrancesco et al., 2017)
Macrophage activation syndrome (Gattorno et al., 2008b; Miettunen et al., 2012; Rajasekaran et al., 2014; Vastert et al., 2014; Sonmez et al., 2018)
Sweet's syndrome/neutrophilic dermatoses (Delluc et al., 2008; Kluger et al., 2011; Pazyar et al., 2012; Belani et al., 2013)
Neutrophilic panniculitis (Behrens et al., 2006; Aronson and Worobec, 2010; Lipsker et al., 2010)
Erdheim–Chester/histiocytoses (Aouba et al., 2010; Diamond et al., 2016; Tomelleri et al., 2018)
SAPHO (Colina et al., 2010; Eleftheriou et al., 2011; Wendling et al., 2012)
PFAPA (Stojanov et al., 2011; Cantarini et al., 2012a)
Multicentric Castleman disease (Galeotti et al., 2008)
Jessner–Kanof disease (Sparsa et al., 2012)
Primary Sjögren syndrome fatigue (Norheim et al., 2012)
Kawasaki disease (Cohen et al., 2012)
Colitis in chronic granulomatous disease (van de Veerdonk et al., 2011)
Hidradenitis suppurativa (Tzanetakou et al., 2016)
Autoimmune inner ear disease (Vambutas et al., 2014)

Cavalli G and Dinarello CA (2018) Front. Pharmacol. 9:1157

ANAKINRA

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.

COVID-19
Το Kineret ενδείκνυται για τη θεραπεία της νόσου του κορωνοϊού 2019 (COVID-19) σε ενήλικες ασθενείς με πνευμονία που απαιτούν συμπληρωματικό οξυγόνο (οξυγόνο χαμηλής ή υψηλής ροής), οι οποίοι διατρέχουν κίνδυνο εξέλιξης σε βαριά αναπνευστική ανεπάρκεια που προσδιορίζεται από συγκέντρωση στο πλάσμα του διαλυτού υποδοχέα του ενεργοποιητή του πλασμινογόνου τύπου ουροκινάσης (suPAR) ≥ 6 ng/ml (βλ. παραγράφους 4.2, 4.4 και 5.1).

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.

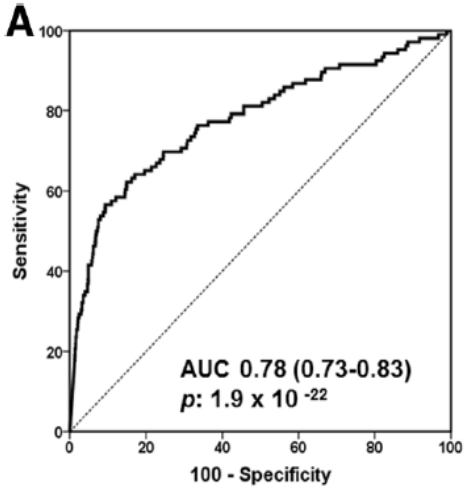
Νόσος του Still
Το Kineret ενδείκνυται για χρήση σε ενήλικες, εφήβους, παιδιά και βρέφη ηλικίας 8 μηνών και άνω με σωματικό βάρος 10 kg και άνω για τη θεραπεία της νόσου του Still, συμπεριλαμβανομένης της συστηματικής νεανικής ιδιοπαθούς αρθρίτιδας (SJIA) και της νόσου του Still των ενηλίκων (AOSD), 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.

Το Kineret μπορεί να χορηγηθεί ως μονοθεραπεία ή σε συνδυασμό με άλλα αντιφλεγμονώδη φάρμακα και νοσοτροποποιητικά αντιρευματικά φάρμακα (DMARD).

Il-1 & SEPSIS

HYPERFERRITINEMIA & SEPSIS

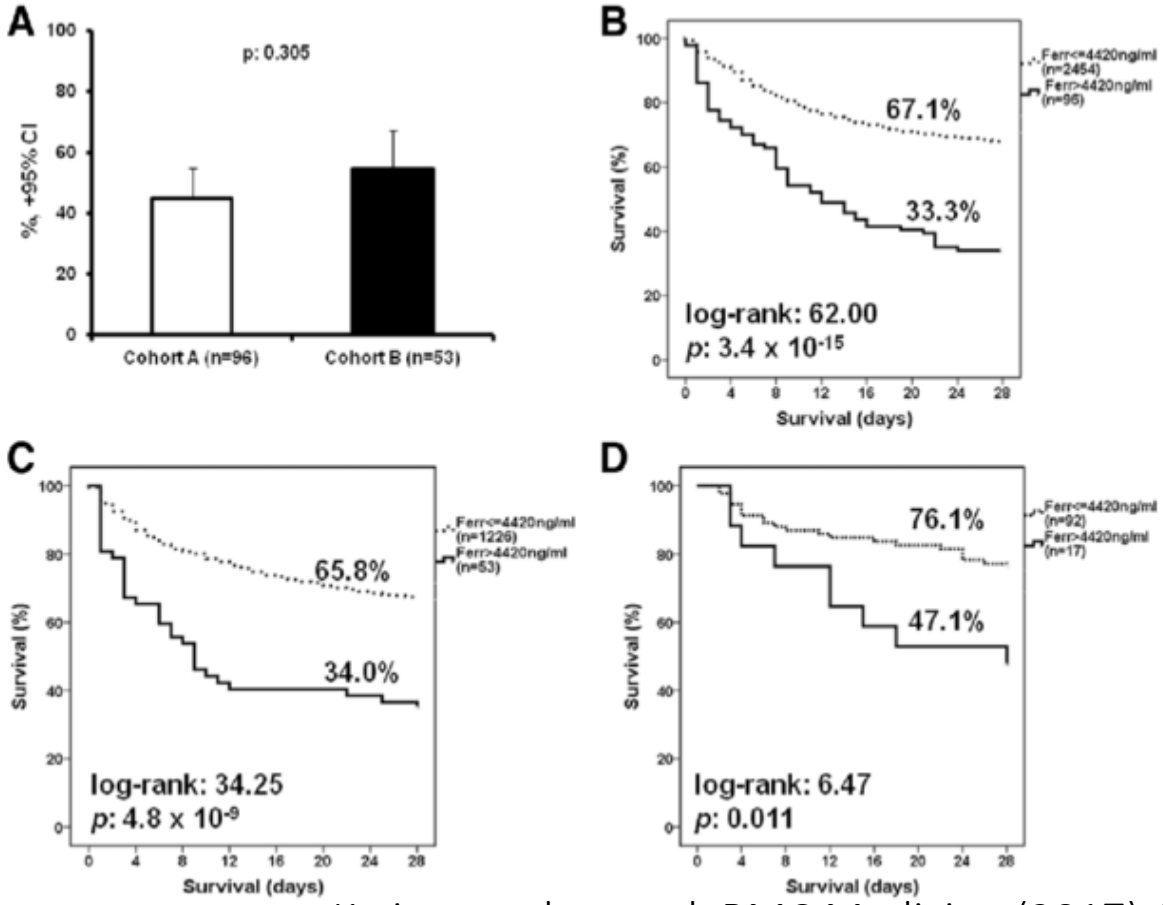
Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis



FERRITIN >4.420 ng/ml

B

	MALS (+) (n patients)	MALS (-) (n patients)	Total
>4,420 ng/ml	31 Sensitivity: 24.2% PPV: 30.7%	70	101
≤4,420 ng/ml	97	3,219 Specificity: 97.9% NPV: 97.1%	3,316
	128	3,289	3,417



Kyriazopoulou et al. BMC Medicine (2017) 15:172

Classification of the currently available strategies of immunointervention in sepsis.

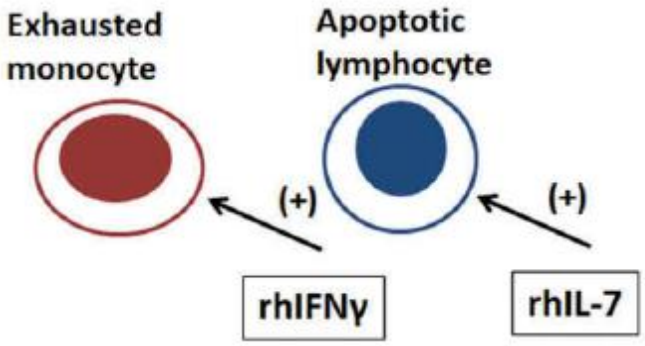
Pharmacological management of sepsis in adults with a focus on the current gold standard treatments and promising adjunctive strategies: evidence from the last five years

Evdoxia Kyriazopoulou & Evangelos J. Giamarellos-Bourboulis

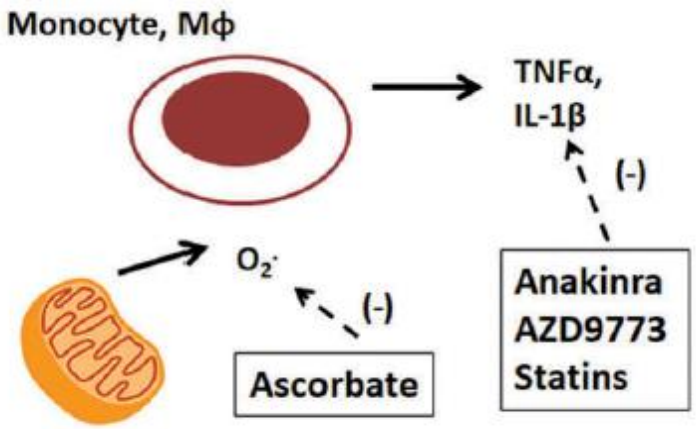
LOW-DOSE HYDROCORTISONE + FLUDROCORTISONE

↓ mortality in CIRCI

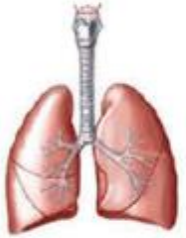
SUPPRESSED HOST RESPONSE



EXAGGERATED HOST RESPONSE



MACROLIDES



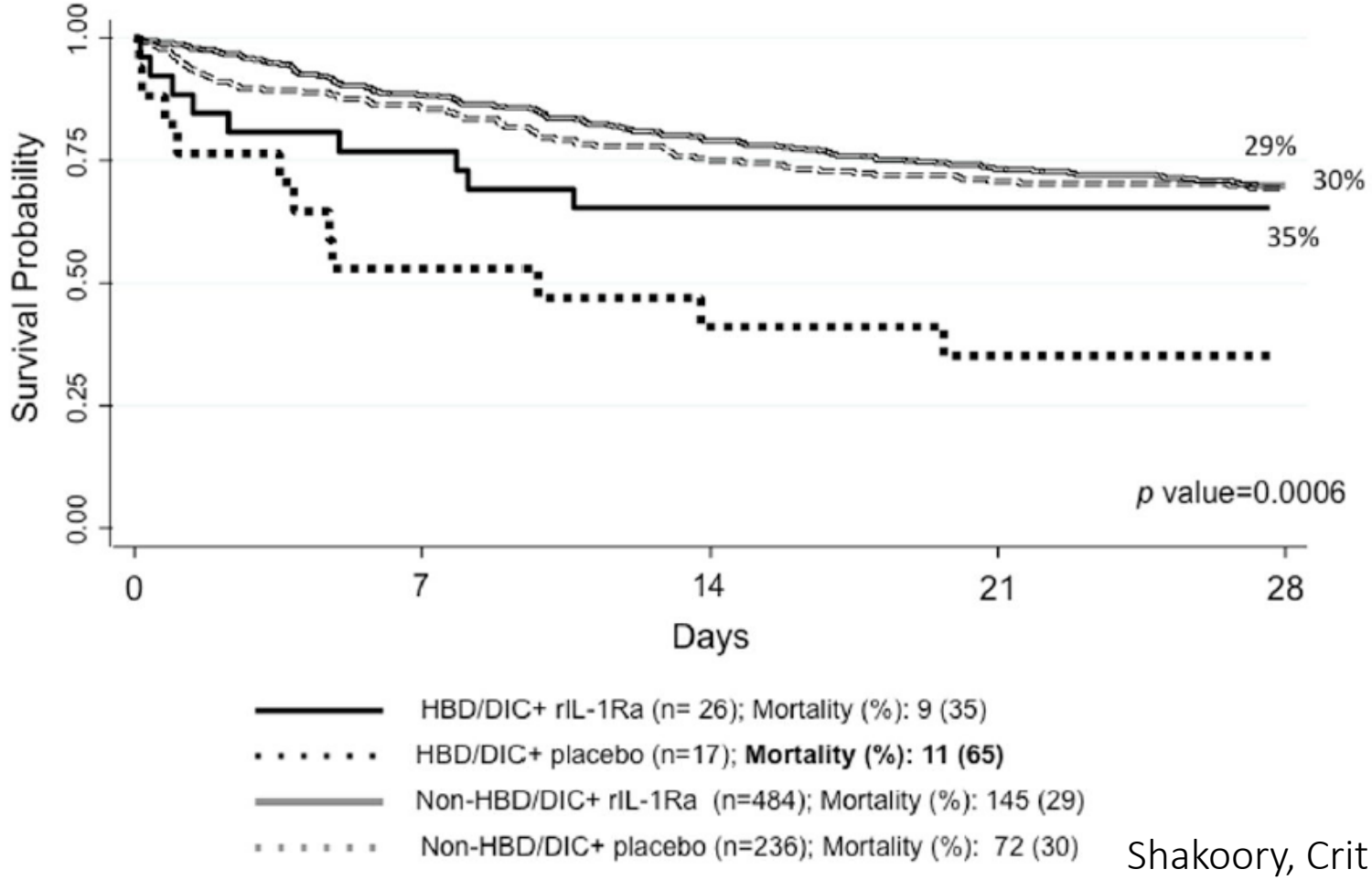
↓ mortality in sCAP

Expert Opinion on Pharmacotherapy, 2019

ANAKINRA IN SEPSIS

Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of the macrophage activation syndrome: Re-analysis of a prior Phase III trial

ΣΗΜΑΝΤΙΚΗ Η ΑΝΑΓΝΩΡΙΣΗ ΤΟΥ ΦΑΙΝΟΤΥΠΟΥ ΤΗΣ ΣΗΨΗΣ



Shakoory, Crit Care Med. 2016 February ; 44(2): 275–281

IMMUNOMODULATION IN SEPSIS-PROVIDE

A Trial of Validation and Restoration of Immune Dysfunction in Severe Infections and Sepsis (PROVIDE)

ClinicalTrials.gov Identifier: NCT03332225

Recruitment Status : Completed
First Posted : November 6, 2017
Last Update Posted : July 29, 2020

Sponsor:
Hellenic Institute for the Study of Sepsis

Information provided by (Responsible Party):
Hellenic Institute for the Study of Sepsis

Hellenic Institute for the Study of Sepsis

Study Description

Brief Summary:
The aim of the study is to conduct one RCT of personalized immunotherapy in sepsis targeting patients who lie either on the predominantly hyper-inflammatory arm or on the predominantly hypo-inflammatory arm of the spectrum of the host response. These patients will be selected by the use of a panel of biomarkers and laboratory findings and they will be randomly allocated to placebo or immunotherapy treatment according to their needs.

Condition or disease	Intervention/treatment	Phase
Sepsis Macrophage Activation Syndrome	Drug: Anakinra Drug: Recombinant human interferon-gamma Drug: Placebo	Phase 2

IMMUNOMODULATION IN SEPSIS–IMMUNOSEP

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U.S. National Library of Medicine
ClinicalTrials.gov

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Home > Search Results > Study Record Detail

Save this study

Personalized Immunotherapy in Sepsis (ImmunoSep)

ClinicalTrials.gov Identifier: NCT04990232

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Recruitment Status : Recruiting
First Posted : August 4, 2021
Last Update Posted : July 14, 2022

See Contacts and Locations

Sponsor:
Hellenic Institute for the Study of Sepsis

Information provided by (Responsible Party):
Hellenic Institute for the Study of Sepsis

Hellenic Institute for the Study of Sepsis

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Go to

Brief Summary:
Aim of ImmunoSep is to assess whether personalized adjunctive immunotherapy directed against a state of either fulminant hyper-inflammation or immunoparalysis is able to change sepsis outcomes. Patients will be selected by a panel of biomarkers and laboratory findings and will be allocated to placebo immunotherapy treatment according to their needs.

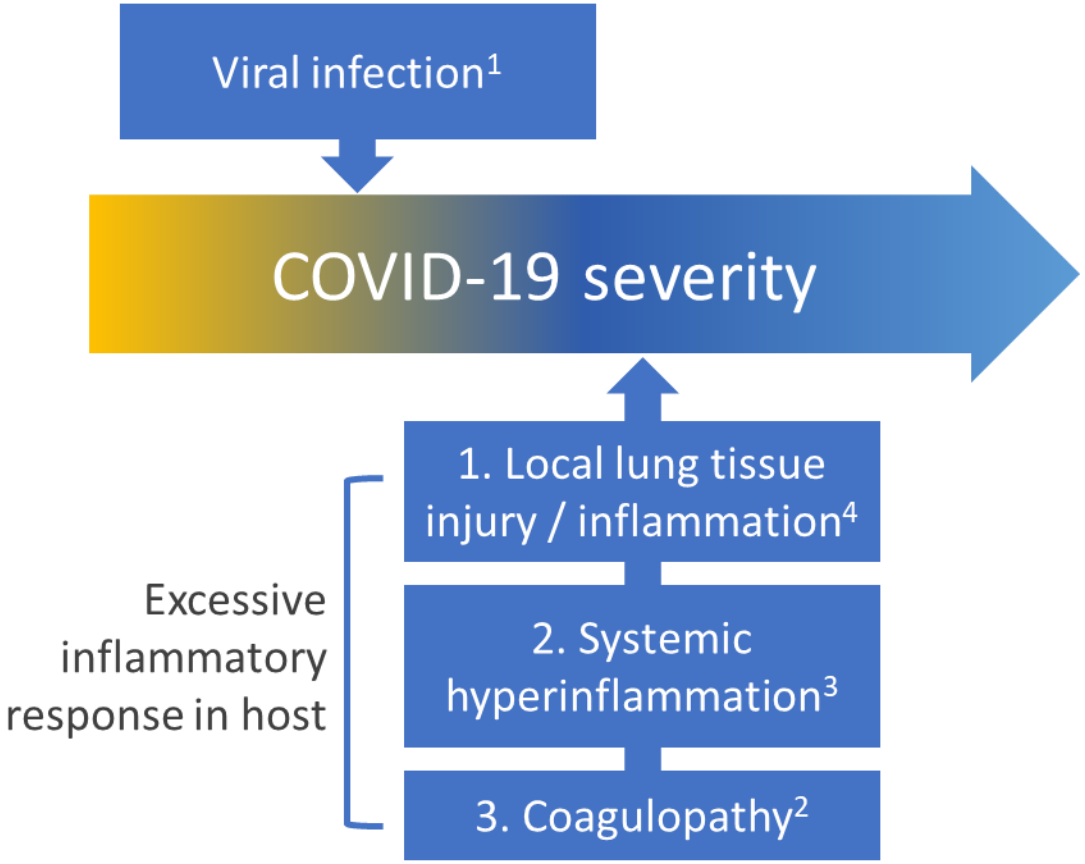
Condition or disease	Intervention/treatment	Phase
Sepsis	Drug: Anakinra or rhIFNγ Drug: Placebo	Phase 2

Il-1 & COVID-19

Both viral and host pathophysiological factors drive COVID-19 severity

- Shifting the focus of emerging data away from the virus and towards the **host inflammatory response**[1]
  - No drug targeting the host inflammatory response has yet been approved to treat patients with COVID-19; **numerous clinical trials are ongoing**[1]

The next three slides examine the three key aspects of host-driven disease pathology in more detail

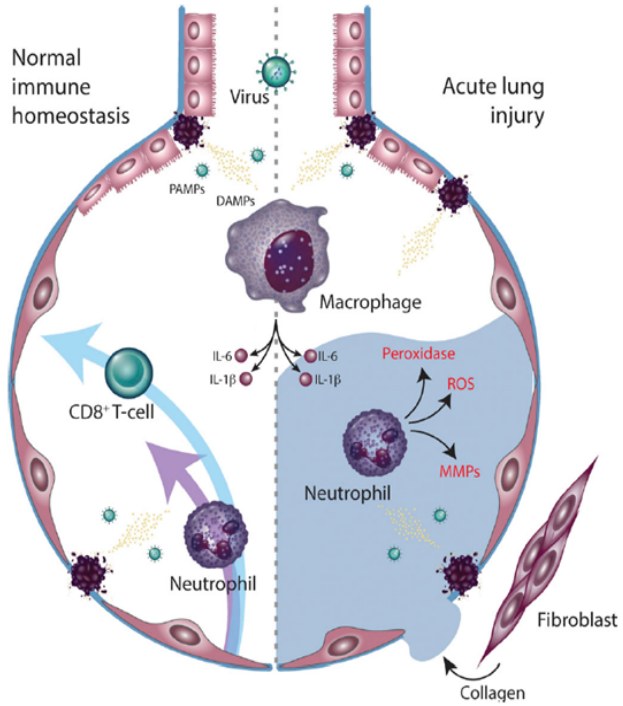


COVID-19, coronavirus disease 2019.

1. Kernan KF & Canna SW. Lancet Rheumatol [Epub 7 May 2020]; 2. McGonagle D, et al. Lancet Rheumatol [Epub 7 May 2020]. 3. Merad M, Martin JC. Nat Rev Immunol [Epub 6 May 2020]; 4. Vardhana SA, Wolchok JD. J Exp Med 2020; 217: e20200678.

Host factors driving COVID-19 severity: 1. Inflammation-driven local lung tissue injury

Innate immune regulation of antiviral defense and tissue toxicity[1]



- Initial **viral infection** and the resulting **pneumocyte lysis** generates PAMPs and DAMPs, which activate tissue-resident macrophages[1]
- Production of cytokines, such as IL-1, and recruitment of **neutrophils, inflammatory monocytes, and CD8⁺ T cells**:[1-4]
  - Control viral growth[1]
  - Induce **tissue damage**, leading to alveolar flooding and fibrosis[1,2]
- Persistent neutrophil-mediated alveolar damage leads to interstitial flooding, ventilation/perfusion mismatching, and **hypoxemic respiratory failure**[1]

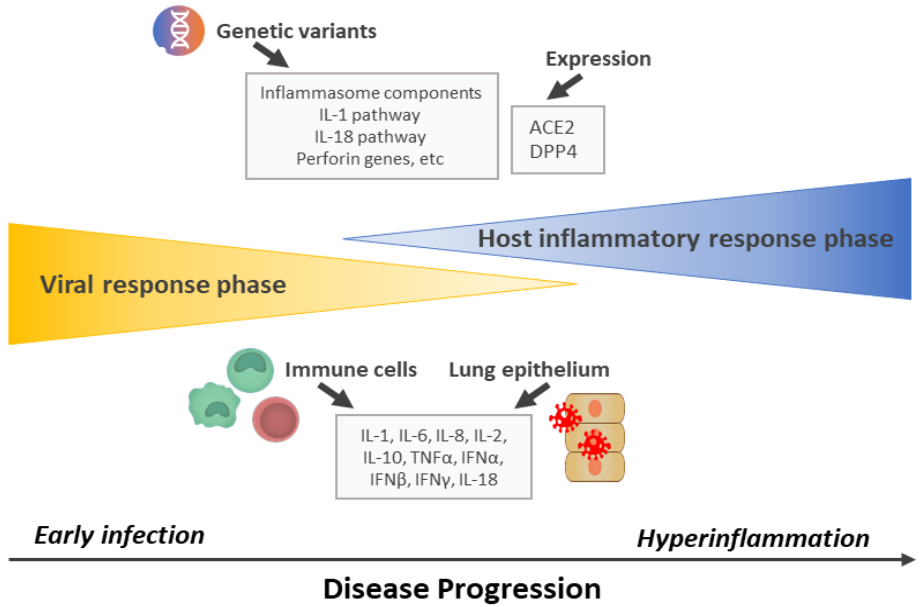
COVID-19, coronavirus disease 2019; DAMPs, damage-associated molecular patterns; MMPs, matrix metalloproteases; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species.

1. Vardhana SA, Wolchok JD. J Exp Med 2020; 217: e20200678; 2. Jamilloux Y, et al. Autoimmun Rev 2020; 19: 102567; 3. Barnes BJ, et al. J Exp Med 2020; 217: e20200652. 4. Merad M, Martin JC. Nat Rev Immunol [Epub 6 May 2020].

Host factors driving COVID-19 severity: 2. Systemic hyperinflammation

- Patients with severe COVID-19 present with signs of **MAS/sHLH-like systemic hyperinflammation**:[1,2]
  - High serum levels of inflammatory cytokines and chemokines[2]
  - Elevated blood inflammatory markers (e.g. CRP, ferritin), but less extreme values than those seen in other sHLH/MAS contexts[2]
  - Lymphopenia[2]
- Widespread hyperinflammation may lead to **multi-organ damage**[3]
  - Elevated ferritin and IL-6 correlate with mortality[4]
  - Elevated CRP correlates with disease severity[5]
- Ongoing studies are evaluating **immunomodulators** in the treatment of COVID-19[6]

COVID-19 disease progression and potential molecular factors involved in an exaggerated inflammatory response[7]

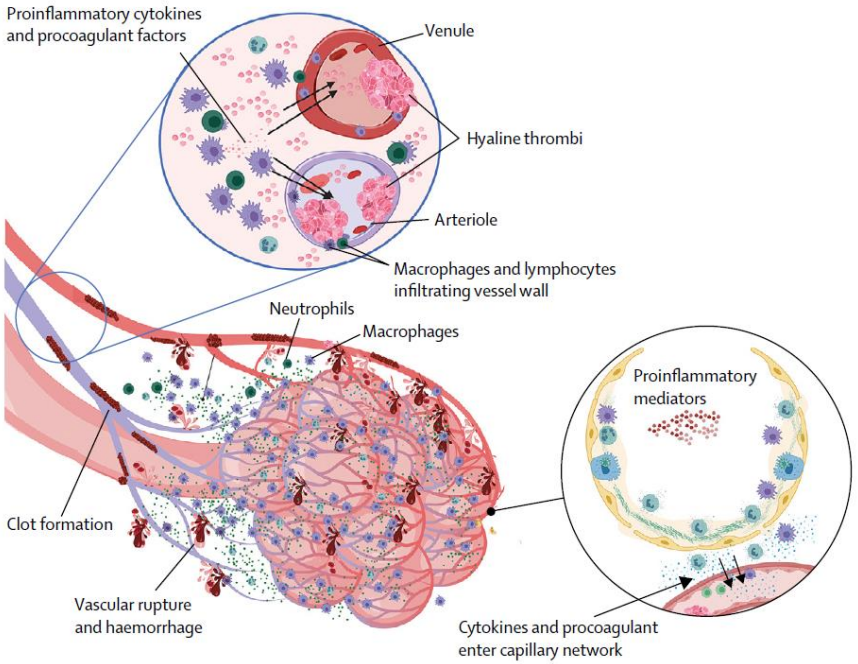


COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DPP4, dipeptidyl peptidase 4; IFN, interferon; IL, interleukin; MAS, macrophage activation syndrome; sHLH secondary hemophagocytic lymphohistiocytosis; TNF, tumor necrosis factor.

1. McGonagle D, et al. Autoimmun Rev 2020; 19: 102537; 2. Jamilloux Y, et al. Autoimmun Rev 2020; 19: 102567; 3. Tay MZ, et al. Nat Rev Immunol 2020; 20: 363-74; 4. Mehta P, et al. Lancet 2020; 395: 1033–4; 5. Xu G, et al. Clin Rev Allergy Immunol [Epub 24 Apr 2020]; 6. Henderson LA, et al. Arthritis Rheumatol [Epub 15 Apr 2020]; 7. Colafrancesco S, et al. Autoimmun Rev 2020; 19: 102573.

Host factors driving COVID-19 severity: 3. Pulmonary intravascular coagulopathy

Pulmonary intravascular coagulopathy in COVID-19 pneumonia[1]



- Key features:
  - Elevated levels of fibrin degradation products (D-dimers; reflects pulmonary vascular bed thrombosis with fibrinolysis)[1]
  - Lower platelet counts[1]
  - **Coagulation abnormalities**[1]
  - Pulmonary microvascular **thrombosis** and **haemorrhage**[1]
- This inflammation-driven microthrombotic immunopathology leads to **right ventricular stress** and contributes to **mortality**[1]
  - Risk factors for cardiovascular disease might increase risk of death in severe COVID-19 inflammation[1]
- Role of anticoagulation in the treatment of COVID-19 is being explored[1]

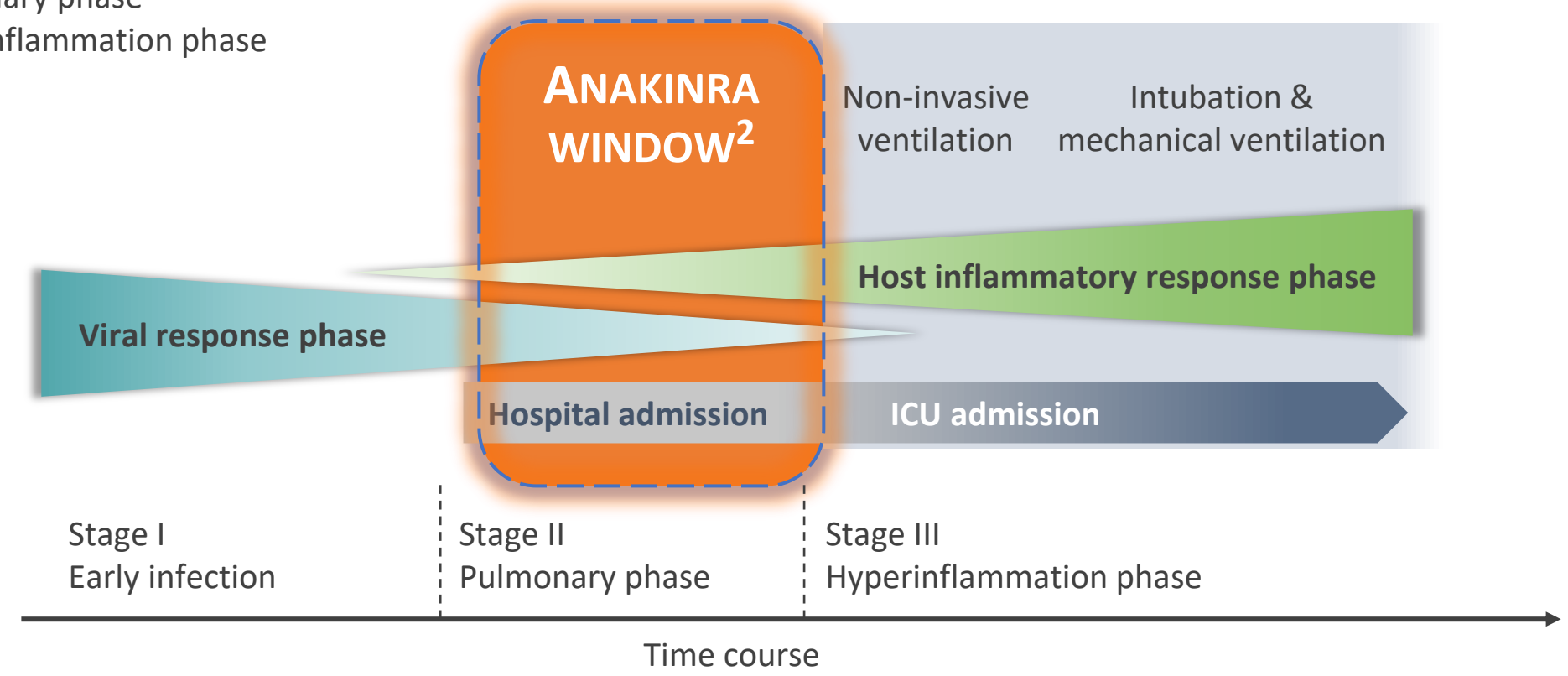
COVID-19, coronavirus disease 2019.

1. McGonagle D, et al. Lancet Rheumatol 2020; 19: 102537. Figure reproduced with permission from McGonagle D, et al. Lancet Rheumatol 2020; 19: 102537.

ANAKINRA WINDOW

Infection with SARS-CoV-2 (COVID-19) can be classified into **three clinical stages of increasing severity**:[1]

1. Early infection
2. Pulmonary phase
3. Hyperinflammation phase

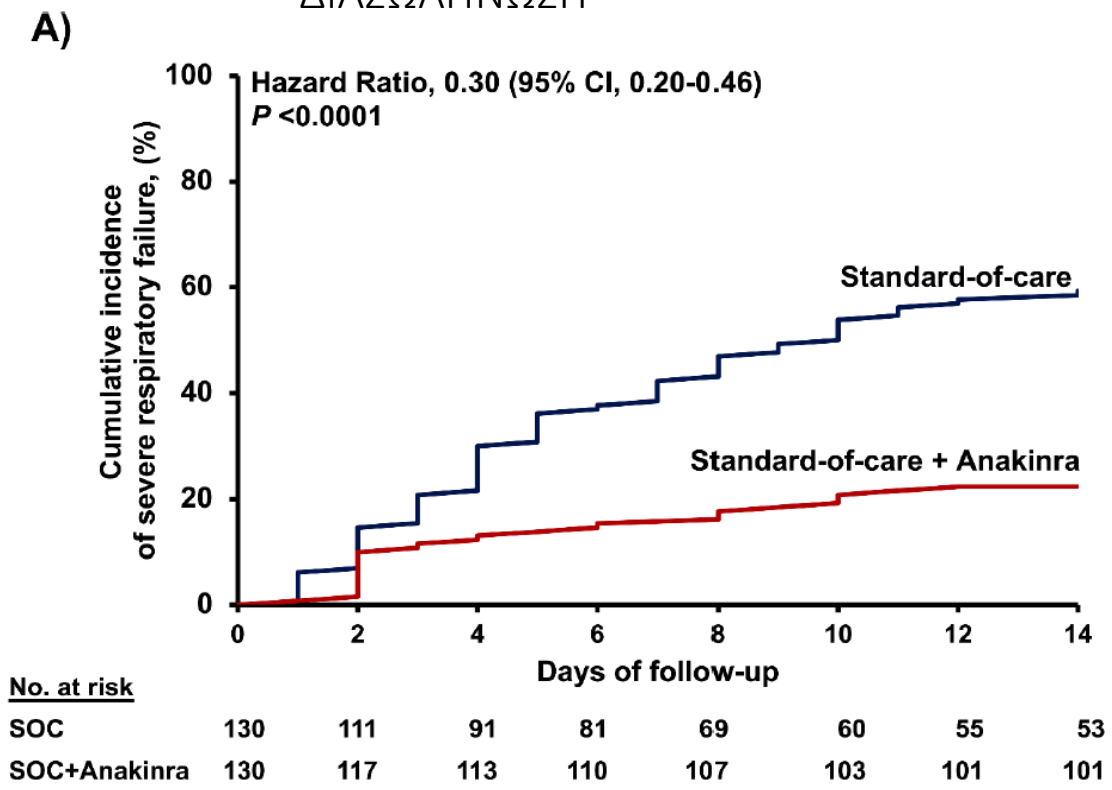


1. Siddiqi HK, Mehra MR. *J Heart **Lung** Transplant* 2020;39:405-407. 2. Kyriazopoulou et al. Nat Med 2021.

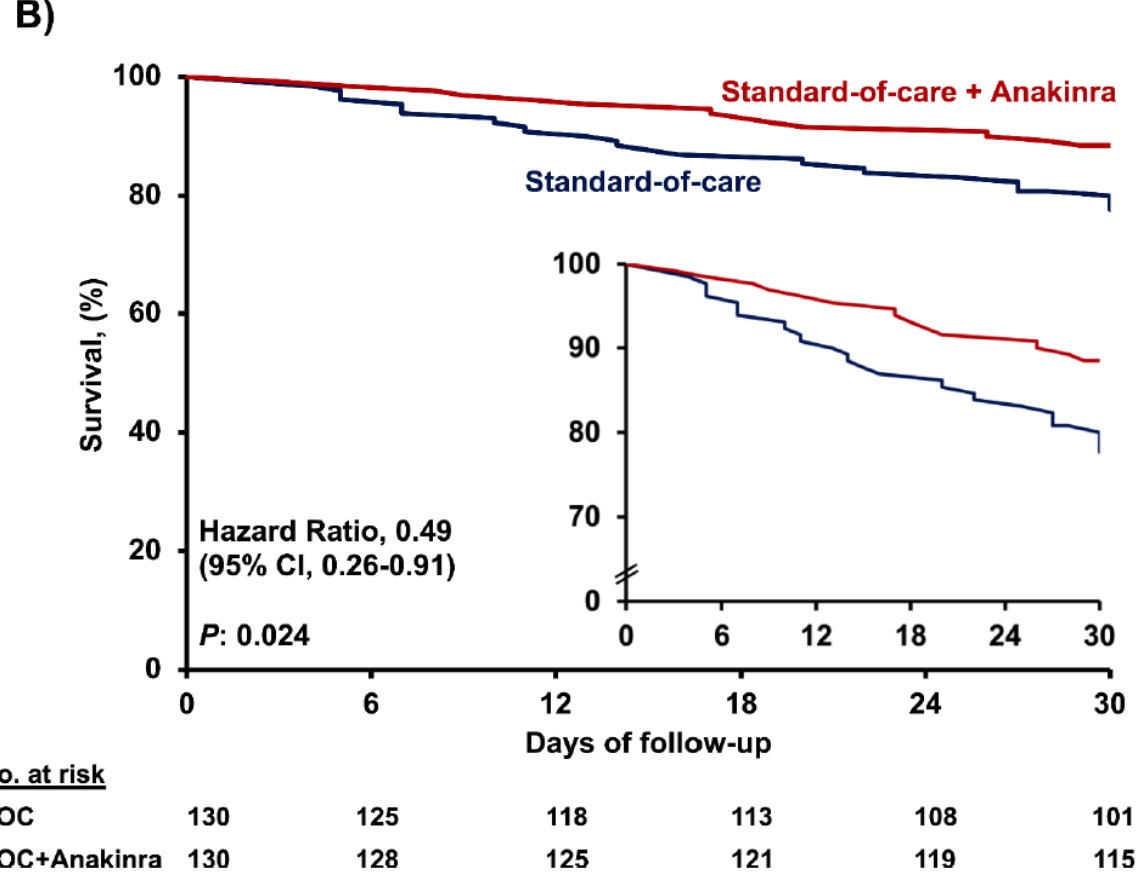
ANAKINRA & COVID-19: SAVE

An open label trial of anakinra to prevent respiratory failure in COVID-19

ΔΙΑΣΩΛΗΝΩΣΗ

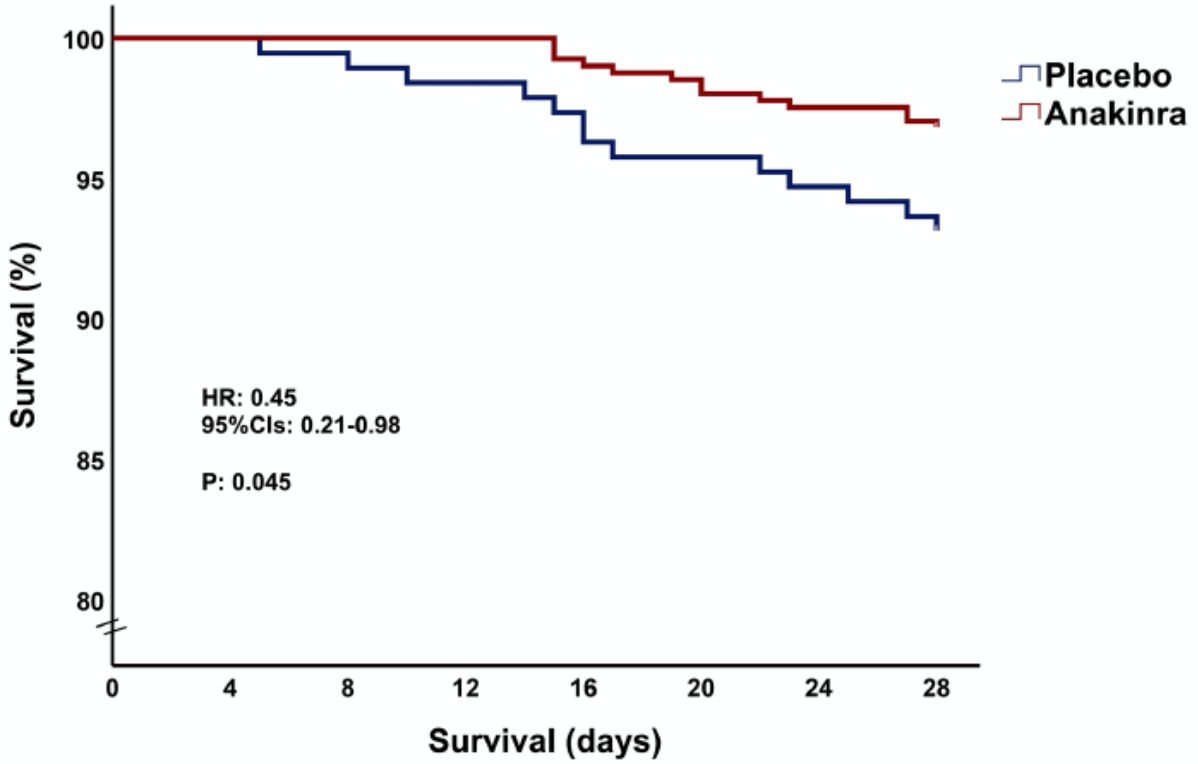


ΘΑΝΑΤΟΣ

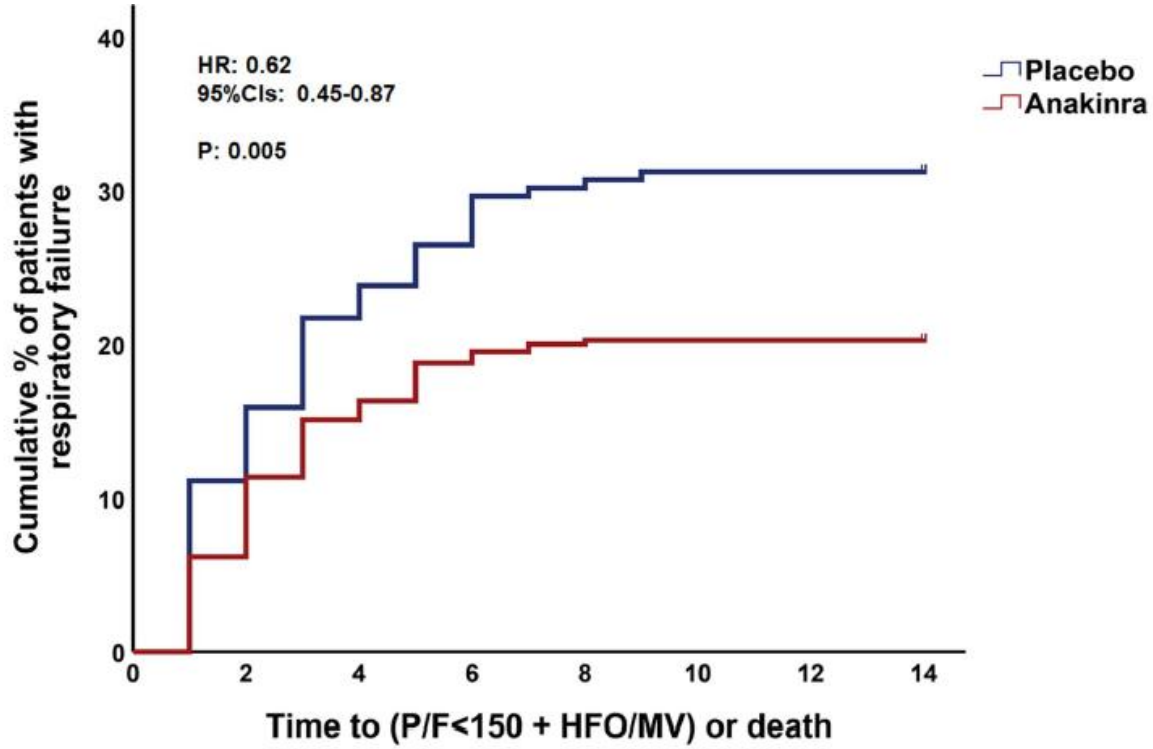


Kyriazopoulou et al. eLife 2021;10:e66125

ANAKINRA & COVID-19: SAVE-MORE



Patients at risk (n)								
Placebo	189	189	187	186	182	181	179	176
Anakinra	405	405	405	405	401	397	395	392



Patients at risk (n)								
Placebo	189	159	144	133	131	130	130	129
Anakinra	405	359	339	326	323	323	323	321

Kyriazopoulou, Nature Medicine VOL 27 , 2021 1752–1760

su-PAR

Prognostic Role of Soluble Urokinase Plasminogen Activator Receptor at the Emergency Department: A Position Paper by the Hellenic Sepsis Study Group

Table 1 Expert position on the strengths and weaknesses of soluble urokinase plasminogen activator receptor (suPAR) for the prognosis of patients at the emergency department (ED)

Reference	Strengths
[10]	Concentrations > 6 ng/ml have high sensitivity for unfavourable outcome and signify considerable risk of death for patients admitted to the ED
[11]	Concentrations < 4 ng/ml have high NPV for unfavourable outcome and allow discharge of the patient from the ED
[14]	Concentrations < 12 ng/ml for patients with infections and systemic inflammatory response syndrome have high NPV for unfavourable outcome after 28 days

Reference	Limitations
[1]	Non-specific for certain disease entities
[3–6]	Comorbidities such as chronic renal disease, HIV infection, solid tumour malignancy increase baseline levels
[10]	Concentrations between 4 and 6 ng/ml do not clearly indicate the risk of unfavourable outcome for patients admitted to the ED

Velissaris, Infect Dis Ther (2020) 9:407–416

IL-1 & COVID-19 SCOPE SCORE

Cell Reports Medicine

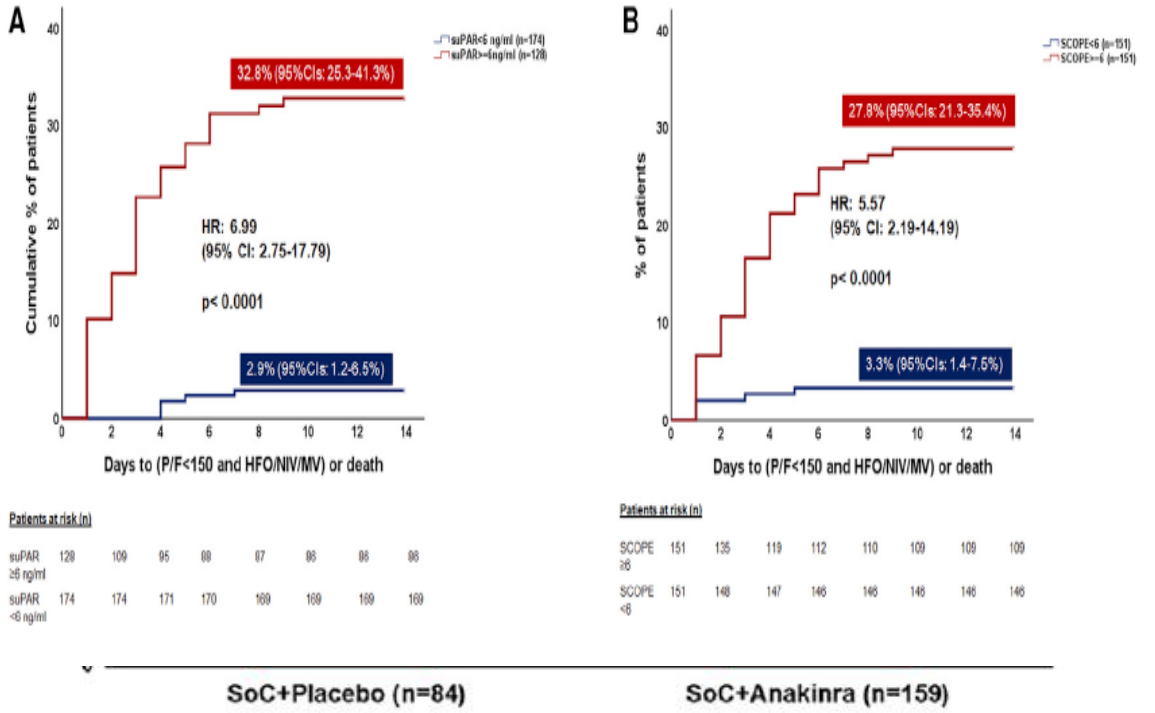
Article

Development and validation of SCOPE score: A clinical score to predict COVID-19 pneumonia progression to severe respiratory failure

Table 1. The SCOPE score

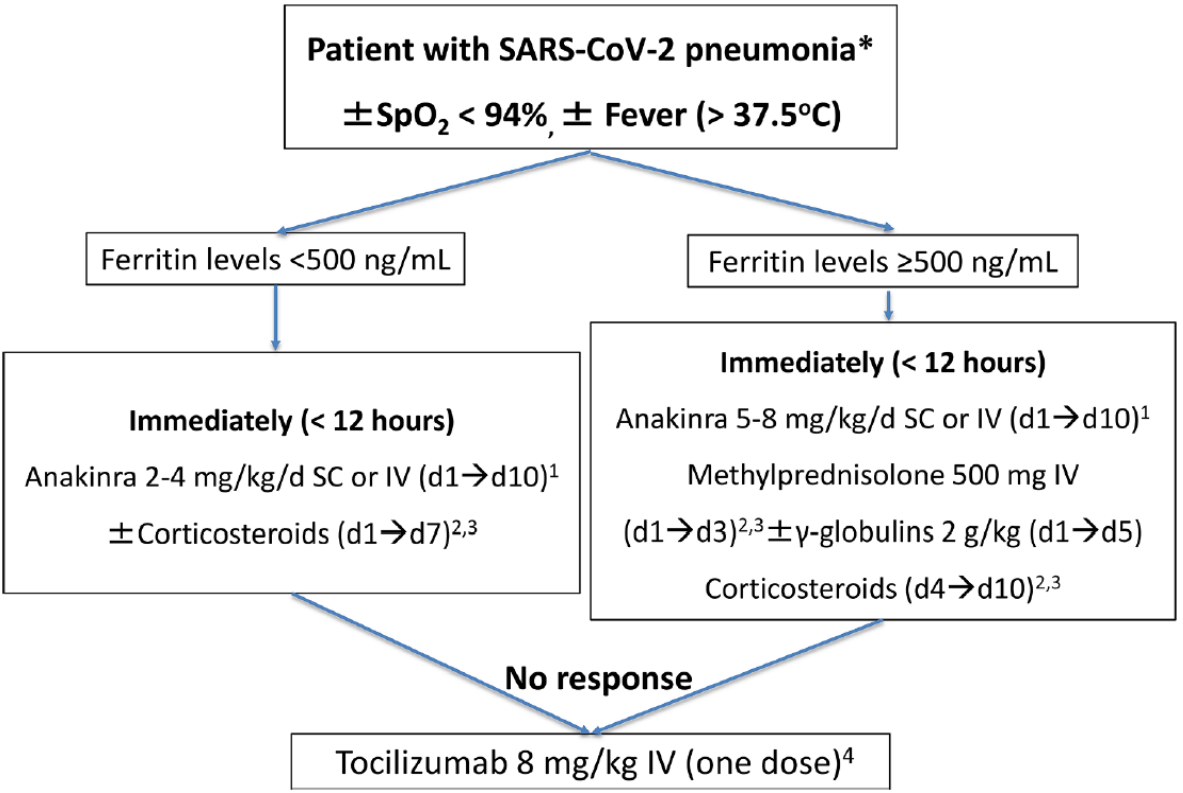
D-dimers (mg/L)	CRP (mg/L)	Ferritin (ng/mL)	IL-6 (pg/mL)	Points
0.10–0.40	0.3–25.0	10–225.0	0.7–5.0	0
>0.40–0.57	>25.0–45.0	>225.0–450.0	>5.0–12.0	1
>0.57–0.90	>45.0–85.0	>450.0–750.0	>12.0–30.0	2
>0.90	>85	>750	>30	3

Each of the four biomarkers is allocated 0 to 3 points according to the concentration. The final score is the sum of the points provided by each biomarker.



Giamarellos-Bourboulis et al., 2022, Cell Reports Medicine 3, 100560

Lessons from pathophysiology: Use of individualized combination treatments with immune interventional agents to tackle severe respiratory failure in patients with COVID-19



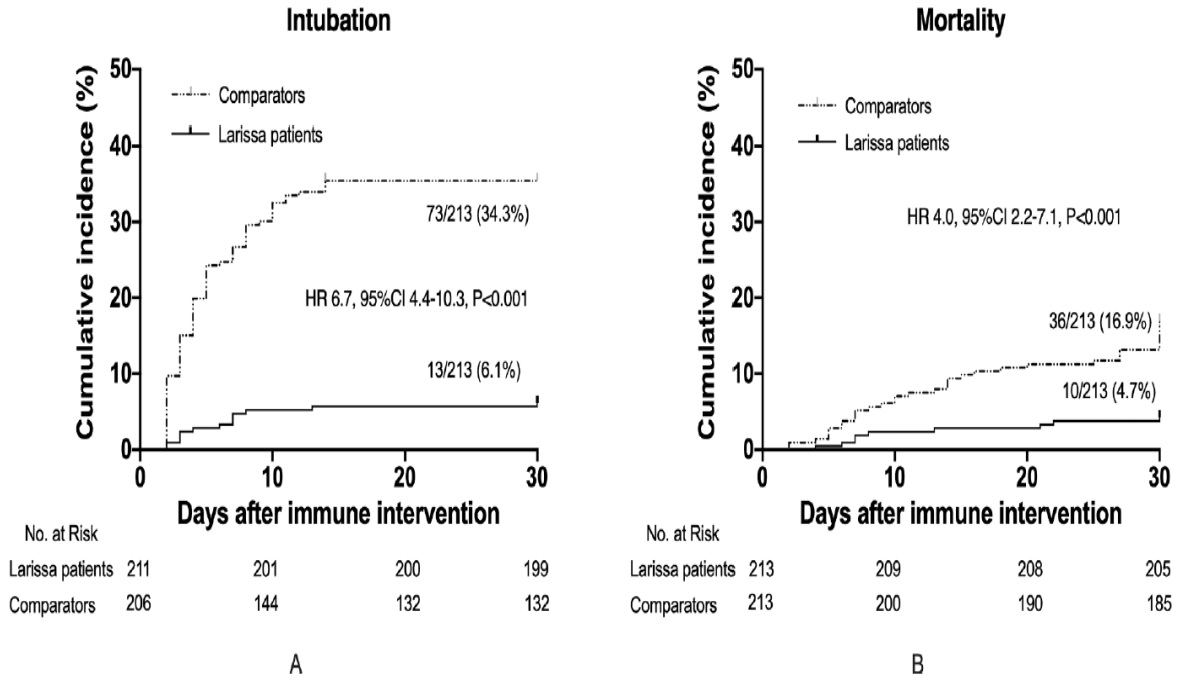


Fig. 5. Kaplan-Meier analyses of efficacy outcomes of "Larissa patients" and "Comparators". (A) Intubation: Analysis includes 86 events-intubations in total. Patients who died before intubation were excluded (2 from "Larissa patients" and 7 from "Comparators"). (B) Mortality: Analysis includes 46 events-deaths in total. Data from patients who were event-free at the end of follow-up were censored at 30 days (one death occurred at 58th day of hospitalization in ICU).

Ntalekos, European Journal of Internal Medicine 88 (2021) 52–62

Il-1 & CYTOKINE STORM

CYTOKINE STORM- HLH/MAS

Recommendations for the management of hemophagocytic lymphohistiocytosis in adults

Table 1. Causes of primary and secondary HLH

Primary HLH (Mendelian inherited conditions leading to HLH) (Table 4)

- Defects in the cytolytic function of cytotoxic T cells and/or NK cells[13,46,51]
- Defects in inflammasome regulation[122,123]

Secondary HLH (apparently non-Mendelian HLH)[10]

- Infections (mainly viruses, such as EBV, HIV, and CMV, but also bacteria, parasites, and fungi)[14]
- Malignancies (mainly malignant lymphoma)[15]
- Macrophage activation syndrome in autoinflammatory or autoimmune disorders[111]
- Other causes (organ or stem cell transplantation; metabolic, traumatic, iatrogenic [immunosuppression, vaccination, surgery, hemodialysis] causes; and, rarely, pregnancy)[10,14]

Table 2. HLH-2004 diagnostic criteria

The diagnosis of HLH can be established if Criterion 1 or 2 is fulfilled.
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood)
Hemoglobin <90 g/L (hemoglobin <100 g/L in infants <4 wk)
Platelets $<100 \times 10^9$/L
Neutrophils $<1.0 \times 10^9$/L
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)
Fibrinogen ≤1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy.
Low or no NK cell activity (according to local laboratory reference)
Ferritin ≥500 μg/L
sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

Rosee Blood 2019;133(23):2465

NHS DEFINITIONS

Haemophagocytic Lymphohistiocytosis (HLH)	A rare condition and comprises a syndrome of severe, uncontrolled, self-perpetuating inflammation or hyperinflammation causing multi-organ failure with a very high mortality rate.
Primary (pHLH)	A genetic immune system defect usually identified in infants or childhood leading to a failure of immune regulation and hyperinflammation
Secondary HLH (sHLH)	Results from a trigger from another disease process leading to uncontrolled, pathological inflammation (hyperinflammation). Most commonly this is cancer (malignancy), infection (sepsis) or rheumatological disease
Macrophage Activation Syndrome (MAS)	sHLH triggered by rheumatic disease
Macrophage Activation Like Syndrome in Sepsis (MALS)	sHLH triggered by sepsis
Cytokine storm syndrome (CSS)	This term includes, but is not limited to, HLH (e.g., may also refer to MALS, CRS, MAS)
Cytokine release syndrome (CRS)	sHLH triggered by CART cell therapy
Hyperferritinaemic syndrome	Synonym for any cause of HLH

HLH/MAS

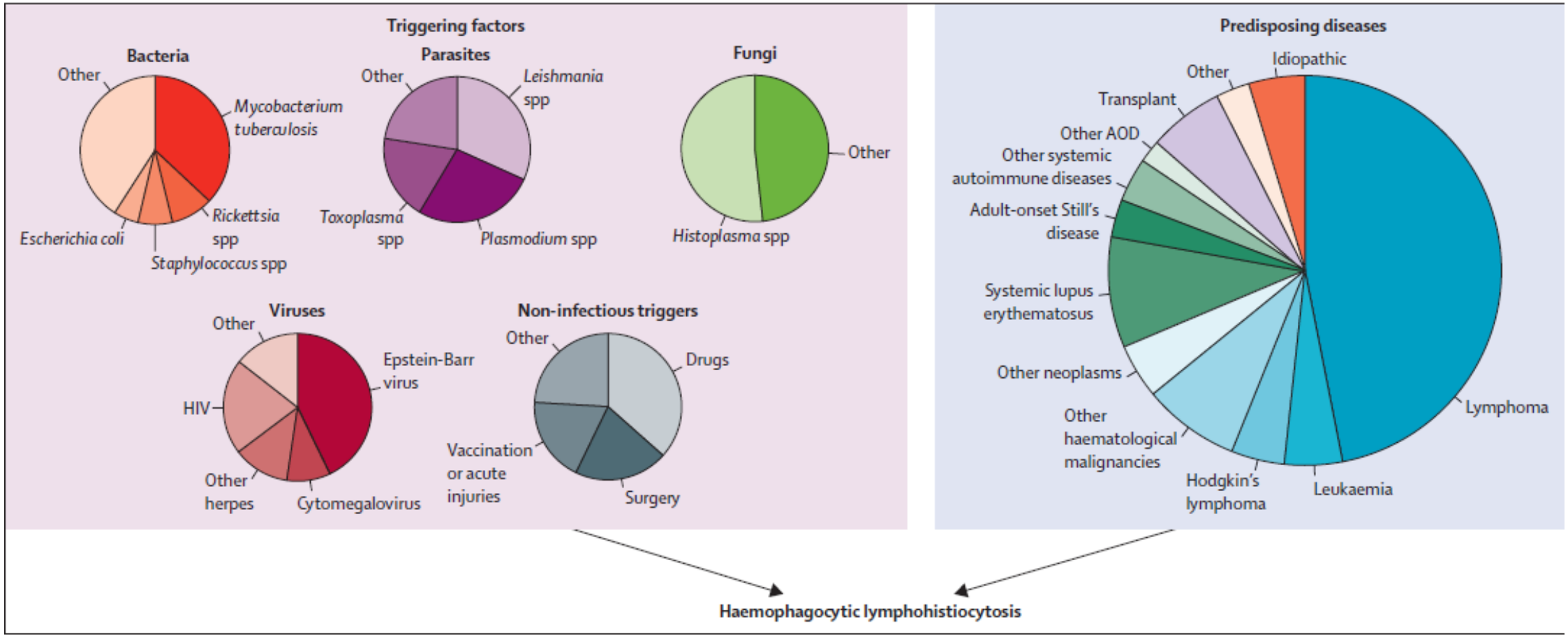


Figure 2: **Main triggering factors and predisposing diseases of haemophagocytic lymphohistiocytosis in 2197 cases reported in adults (panel 1)**

Ramos- Casal Lancet 2014; 383

CYTOKINE STORM

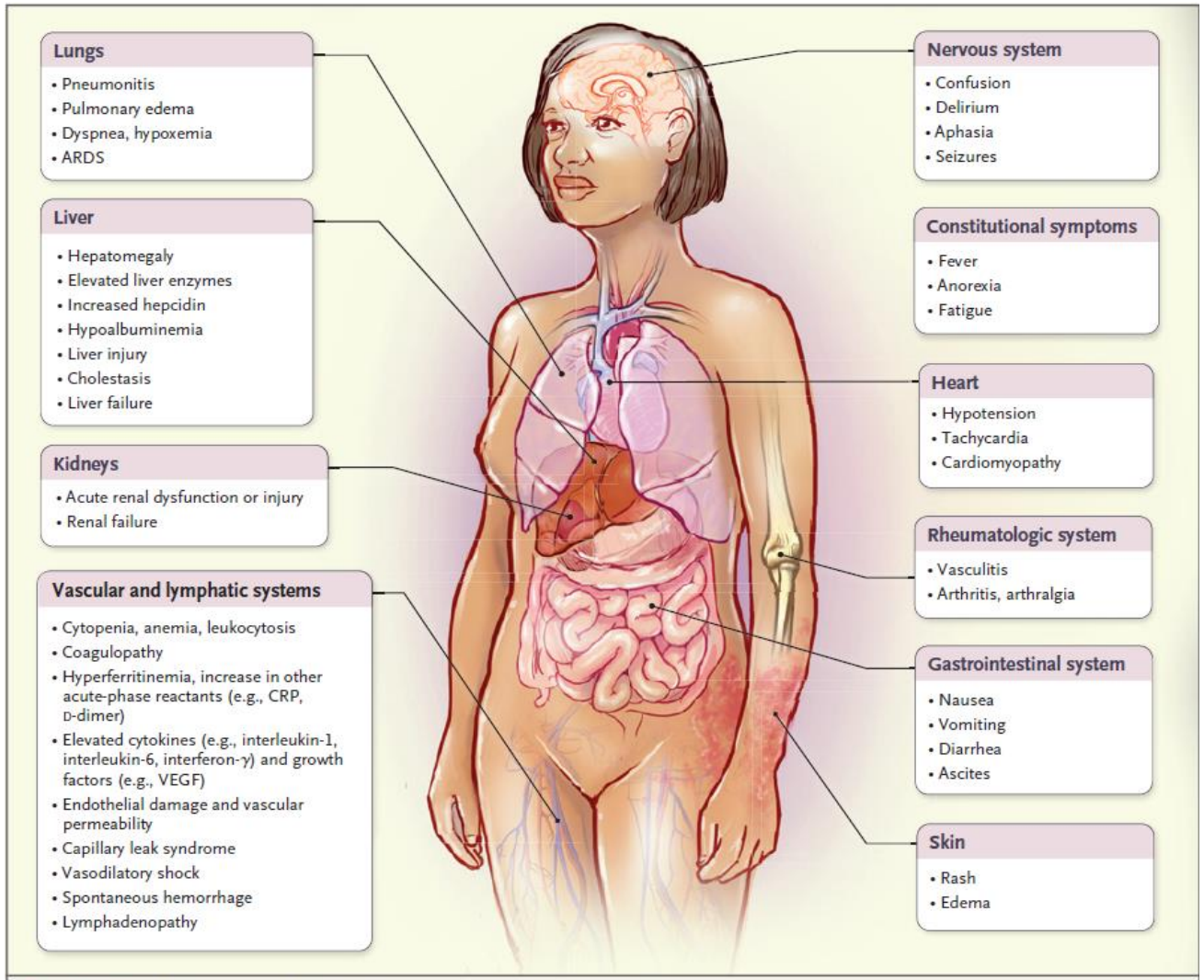


Figure 1. Clinical Presentation of Cytokine Storm.

A wide range of clinical and laboratory abnormalities can be observed in cytokine storm. However, all cases involve elevated circulating cytokine levels, acute systemic inflammatory symptoms, and secondary organ dysfunction (often renal, hepatic, or pulmonary). ARDS denotes acute respiratory distress syndrome, CRP C-reactive protein, and VEGF vascular endothelial growth factor.

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cytokine Storm

David C. Fajgenbaum, M.D., and Carl H. June, M.D.

ΚΛΙΝΙΚΕΣ ΕΚΔΗΛΩΣΕΙΣ

Fajgenbaum N Engl J Med 2020;383:2255-73

HLH/MAS

Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome

The term cytokine storm syndromes describes conditions characterised by a life-threatening, fulminant hypercytokinaemia with high mortality.

Cytokine storm syndromes can be genetic or a secondary complication of autoimmune or autoinflammatory disorders, infections, and haematological malignancies. These syndromes represent a key area of interface between rheumatology and general medicine.

Rheumatologists often lead in management, in view of their experience using intensive immunosuppressive regimens and managing cytokine storm syndromes in the context of rheumatic disorders or infection (**known as secondary haemophagocytic lymphohistiocytosis or macrophage activation syndrome [sHLH/MAS**]).

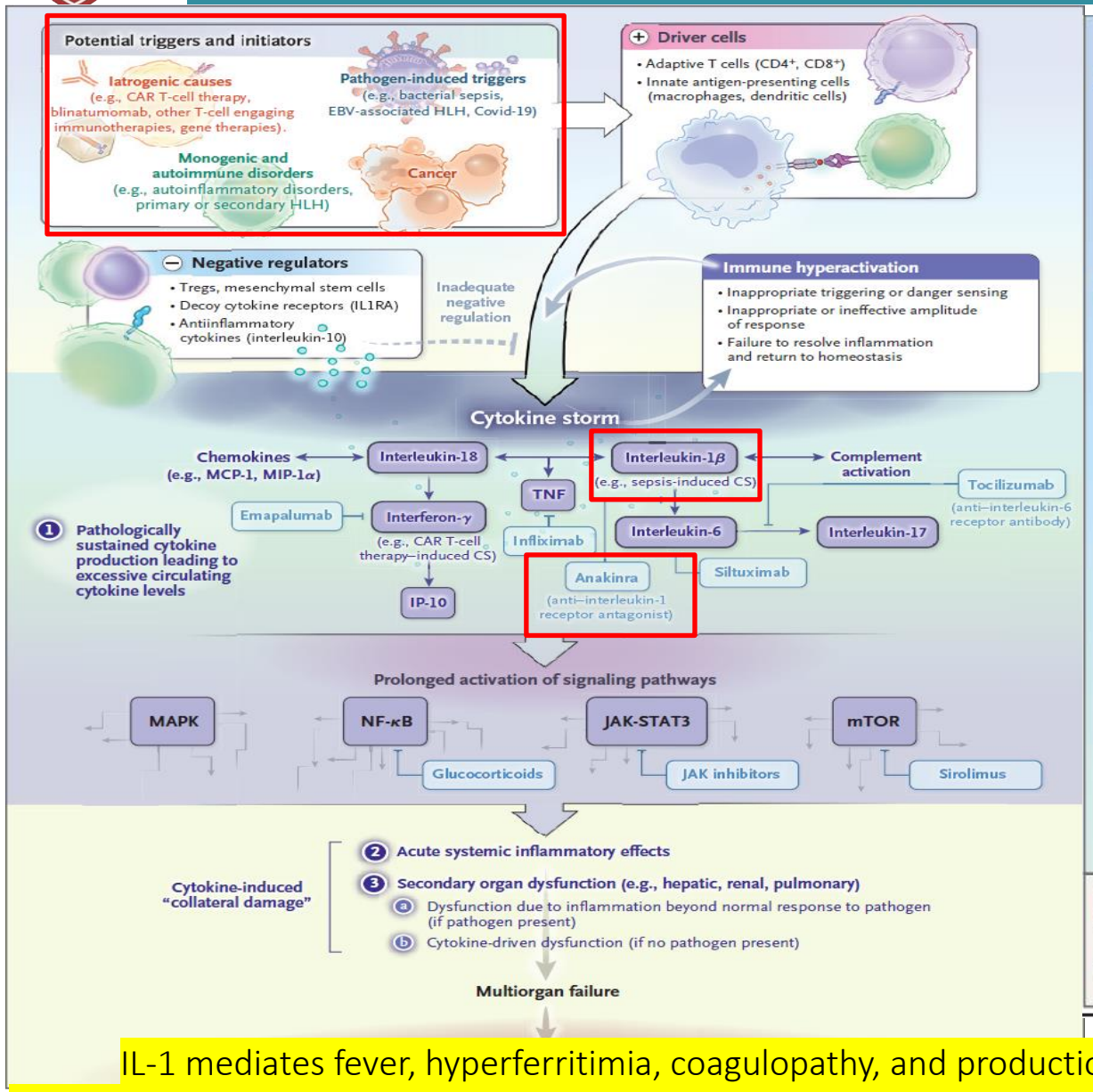
Interleukin (IL)-1 is pivotal in hyperinflammation.

Anakinra, a recombinant humanised IL-1 receptor antagonist, is licenced at a dose of 100 mg once daily by subcutaneous injection for rheumatoid arthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, and cryopyrin-associated periodic syndromes.

In cytokine storm syndromes, where there is a **need for higher doses (from 1-2mg/kg/day – 8 mg/kg/day),** the subcutaneous route is often problematic, as absorption can be unreliable in patients with critical illness, and multiple injections are needed to achieve the high doses required. As a result, **intravenous anakinra** is used in clinical practice for sHLH/MAS, despite this being an off-licence indication and route of administration.

Mehta, Lancet Rheumatol 2020; 2: 358–67

CYTOKINE STORM



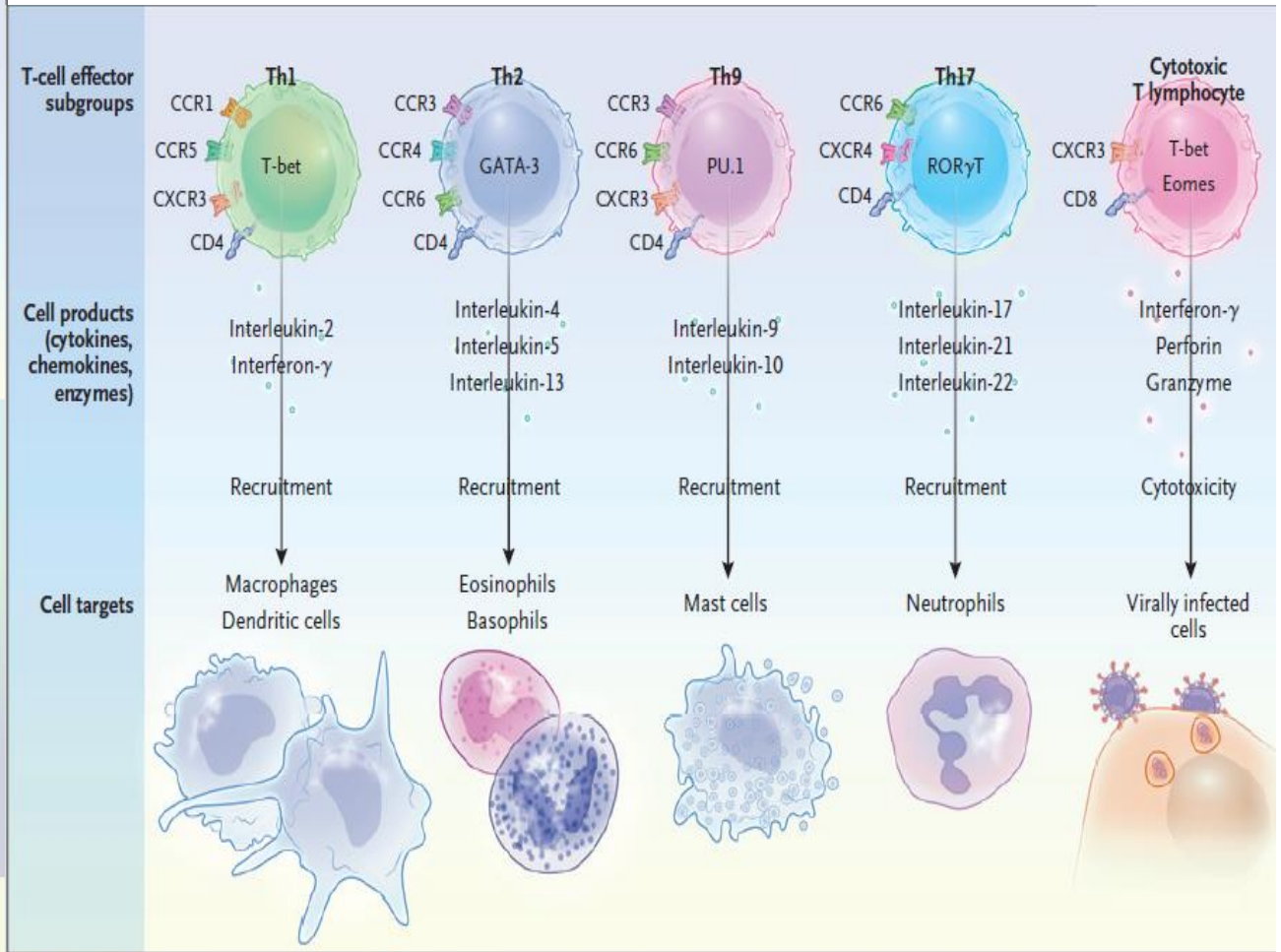


Figure 3. T-Cell Effector Subgroups Involved in Cytokine Storm.

The master transcription factors (T-bet, GATA-3, PU.1, RORγT, and eomesodermin [eomes]), effector molecules, and cell targets are shown for the following T-cell subgroups: types 1, 2, 9, and 17 helper T (Th1, Th2, Th9, and Th17, respectively) cells and cytotoxic T lymphocytes.

IL-1 mediates fever, hyperferritimia, coagulopathy, and production of IL-18;
IL-18 likely mediates hypersplenism, hypertriglyceridemia,hypotension, and elevated IFNg

Fajgenbaum N Engl J Med 2020;383:2255-73

MANAGMEMENT OF CYTOKINE STORM SYNDROMES

Consider in parallel

Switch off the cytokine storm

Induction

First line (consider combination)

Anakinra IV or SC - start within 12 h of sufficient clinical suspicion (unless CRS after CAR T-cell therapy where tocilizumab is indicated)

- Start at least 1-2 mg/kg per day (max 8 mg/kg per day)
- If IV or >100 mg SC daily, administer in divided doses or as continuous IV infusion
- IV route preferred if:
  - High doses (>2 mg/kg per day or >100 mg daily) required
  - Platelets <20 × 10^9/L or haemorrhagic complications
  - SC skin oedema
  - Neurological symptoms

Corticosteroids

- Methylprednisolone 1 g IV daily (or if CNS involvement, dexamethasone 10 mg/m^2 IV daily)
- Avoid or limit if driver unclear (might mask lymphoma diagnosis)

Intravenous immunoglobulin

- 1 g/kg per day for 2 days; consider repeating on day 14

Second line

Etoposide

Intrathecal methotrexate

- If CNS involvement, particularly if lymphoma-driven

Ciclosporin

Maintenance

Consider combination and personalised taper

Anakinra

- Taper down to 100 mg daily and convert IV dosing to SC

Ciclosporin or tacrolimus PO

Corticosteroids PO, at lowest possible dose for shortest duration

+

Treat the underlying cause

Rheumatological

- Autoinflammatory (eg, AOSD or sJIA): biological or conventional DMARDs
- Autoimmune (eg, SLE): consider rituximab or cyclophosphamide

Infection

- Antimicrobials
- If EBV-driven: rituximab
- If multicentric Castleman's disease (HHV8): tocilizumab

Malignancy

- Chemotherapy or immunotherapy

Iatrogenic

- Discontinue culprit drug
- If after CAR T-cell therapy, treat as per guidelines for CRS and tocilizumab

Primary or familial HLH

- Emapalumab (if available)
- HSCT in eligible patients

+

Treat complications

Infection

- Monitor for neutropenic sepsis and opportunistic fungal infections
- Supportive
- General (eg, inotropes, blood products if coagulopathy, or cytopenias)
- Organ specific (eg, renal replacement therapy, ECMO, or assisted ventilation)

+

Prevent complications

Consider prophylaxis for:

- Infection
- Antimicrobials, particularly if neutropenic or cumulative immunosuppression
- Bone protection (when appropriate)

Mehta, Lancet Rheumatol 2020; 2: 358–67

ANAKINRA & HLH

Anakinra for the treatment of adult secondary HLH: a retrospective experience

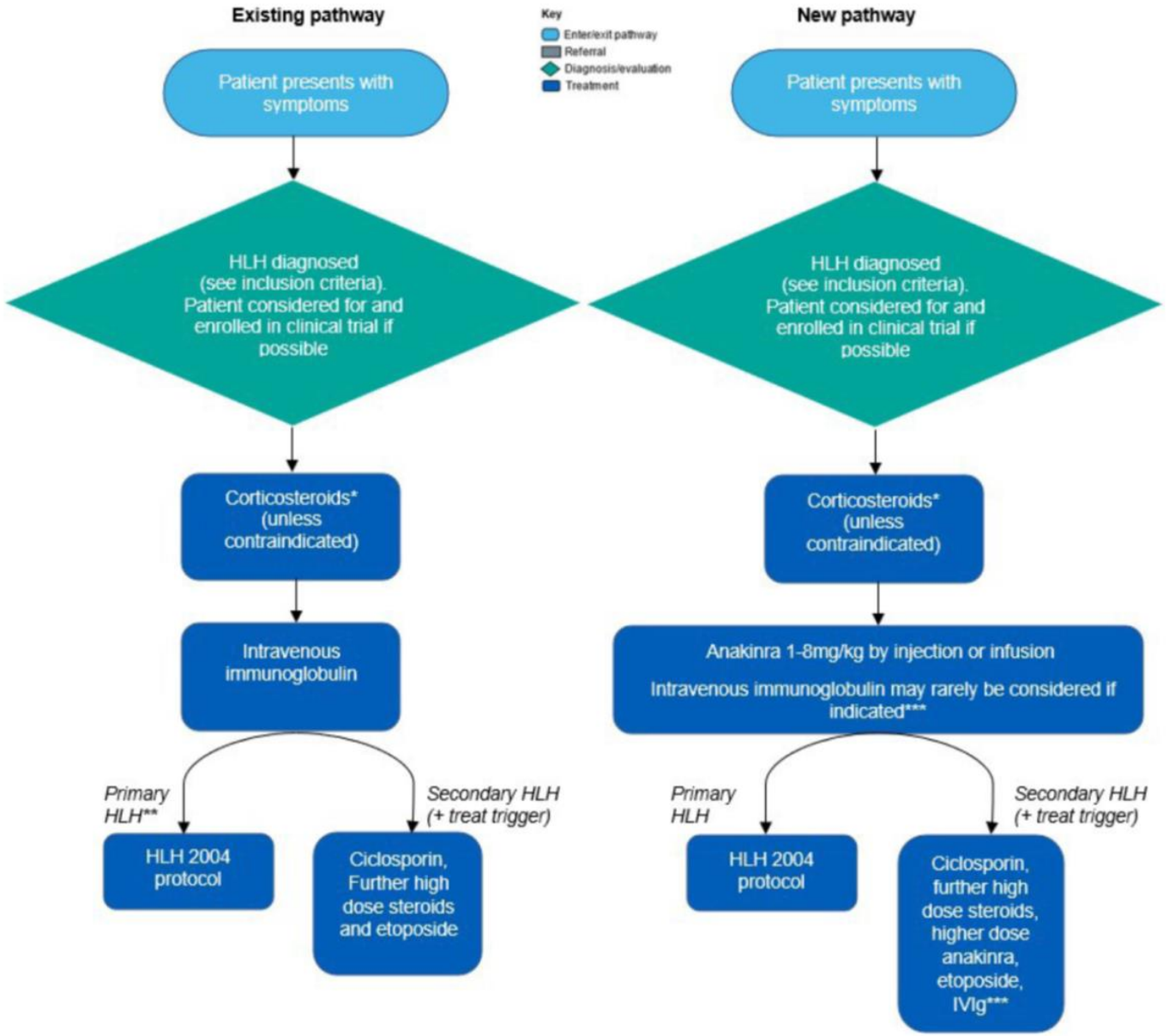
Table 3 Previously described cohorts of adult secondary HLH patients treated with anakinra are summarized

Author, Year	N	Causes of HLH (%)	HLH-Directed Treatments	Outcomes
Dimopoulos, 2020 [22]	8	COVID-19 pneumonia/sepsis (100%)	Anakinra 200 mg IV q8, corticosteroids (dosage unspecified)	Five of 8 patients (63%) survived. This reported OS was higher than historical series of patients with sHLH in sepsis
Kumar, 2017 [18]	13	Autoimmune/rheumatologic (62%), hematologic malignancy (23%), unknown (8%), other (8%)	Anakinra 100 mg subq q12 (given with cyclosporine, IVIG, and corticosteroids in most instances)	Nine of 13 patients (69%) survived, including 7 of 8 (88%) with autoimmune/rheumatologic disease
Monteagudo, 2020 [19]	5	Autoimmune/rheumatologic (80%), unknown (20%) other	Continuous anakinra infusion (up to 2400 mg/d)	Four of 5 (80%) patients survived. Two patients had previously responded poorly to subq anakinra
Sammut, 2020 [20]	4	CMV viremia (25%), hematologic malignancy (25%), rheumatologic (25%), unknown (25%)	Anakinra 100 mg subq daily, with corticosteroids (75%), or with HLH-2004 protocol (25%)	Two of 4 (50%) patients survived
Wohlfarth, 2019 [21]	8	Unknown (38%), hematologic malignancy (25%), autoimmune disease (13%), EBV viremia (13%), other (13%)	Anakinra 100 m–200 mg q8, with IVIG (88%) and/or high-dose CS (62%)	Four of 8 patients (50%) survived hospitalization

CMV cytomegalovirus, *COVID19* coronavirus disease 2019, *CS* corticosteroid, *EBV* Epstein–barr virus, *HLH* hemophagocytic lymphohistiocytosis, *IV* intravenous, *sHLH* hemophagocytic lymphohistiocytosis, *subq* subcutaneous

Naymagon, International Journal of Hematology, 2022

NHS GUIDANCE

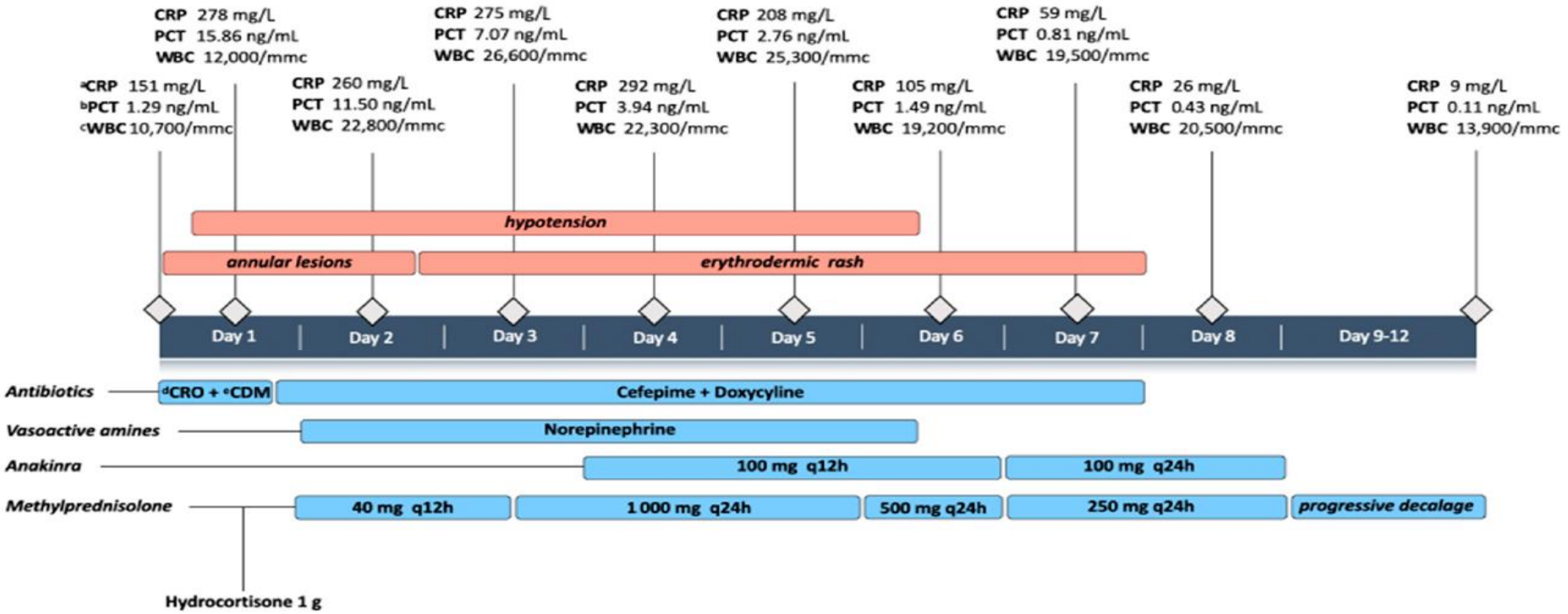


ANAKINRA & MIS-A

Case Report

Multisystem Inflammatory Syndrome in an Adult (MIS-A) Successfully Treated with Anakinra and Glucocorticoids

Paolo Cattaneo [1,2,*], Alessandro Volpe [3], Chiara Simona Cardellino [1], Niccolò Riccardi [1], Giulia Bertoli [1], Tamara Ursini [1], Arjola Ustalli [4], Giovanni Lodi [5], Ivan Daroui [5] and Andrea Angheben [1]



Cattaneo, Microorganisms 2021, 9, 1393

Il-1 & CAR-T-CELL TOXICITY

Clinical efficacy of anakinra to mitigate CAR T-cell therapy–associated toxicity in large B-cell lymphoma

Despite unprecedented efficacy,1 the use of axicabtagene ciloleucel (axi-cel) for the treatment of patients with relapsed or refractory large B-cell lymphoma (LBCL) remains associated with acute toxicity, such as grade $3 cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), occurring in 11% and 32% of patients, respectively

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, y	46	72	60	83	59	76	24	38
Sex	Female	Male	Male	Male	Male	Female	Male	Female
ECOG PS	1	2	0	2	0	1	1	3
Histology	DLBCL	DLBCL	tFL	DLBCL	DLBCL	tFL	DLBCL	DLBCL
Ann Arbor stage	IV	III	IV	IV	IV	III	IV	IV
IPI score	3	4	3	4	3	3	3	4
Prior CNS lymphoma	No	No	No	Yes	No	No	No	No
Previous treatment								
Previous therapies, n	2	2	6	3	3	3	3	4
Refractory disease	No	No	Yes	Yes	No	Yes	Yes	Yes
Previous ASCT	Yes	Yes	Yes	No	Yes	No	No	No
Inflammatory and disease burden markers								
CRP, mg/L	2	13	51	4	232	35	191	214
Ferritin, mg/L	1554	1135	3332	628	14 240	190	8718	6183
LDH > ULN	No	No	No	No	Yes	No	Yes	Yes
Toxicity management								
Treated toxicity	ICANS G4	ICANS G3	ICANS G4	ICANS G4	ICANS G4	ICANS G4	HLH	HLH
Tocilizumab start	Day 4	Day 5	—	Day 4	Day 4	—	Day 3	Day 11
Tocilizumab dose	8 mg/kg IV ×2	8 mg/kg IV ×2	0	8 mg/kg IV ×2	8 mg/kg IV ×2	0	8 mg/kg IV ×1	8 mg/kg IV ×2
Corticosteroid start	Day 4	Day 5	Day 34	Day 5	Day 6	Day 7	Day 3	Day 7
Dexamethasone dose	8-186 mg ×24 d	1-186 mg ×57 d	10 mg ×1 d	40-186 mg ×13 d	40-80 mg ×19 d	4-186 mg ×35 d	12-186 mg ×14 d	40-80 mg ×9 d
Anakinra start	Day 6	Day 41	Day 31	Day 7	Day 10	Day 31	Day 7	Day 14
Anakinra dose	100 mg SC daily ×7	100 mg SC daily ×7	100 mg SC daily ×7	100 mg SC daily ×7	100 mg SC every other day ×5	100 mg SC daily ×7	100 mg SC daily ×7	200 mg SC daily ×1
Response to anakinra								
Toxicity response	Yes (G0)	Yes (G1)	Yes (G0)	Yes (G2)	No	No	No	No
Toxicity recurrence	No	No	No	Yes	Yes	Yes	Yes	Yes
Day of death (cause)	—	Day 80 (pneumonia)	Day 71 (HLH)	Day 18 (PD)	Day 31 (ICH)	Day 51 (ICANS)	Day 17 (PD)	Day 15 (HLH)

No patient had received previous CAR T-cell therapy or ASCT. Seven of 8 patients were admitted to an intensive care unit. One patient had not received corticosteroids, and 2 had not received tocilizumab before initiation of anakinra.
ASCT, autologous stem cell transplantation; CNS, central nervous system; DLBCL, diffuse LBCL; ECOG PS, European Cooperative Oncology Group performance status; G, grade; ICH, intracranial hemorrhage; IPI, International Prognostic Index; PD, progressive disease; tFL, transformed follicular lymphoma; ULN, upper limit of normal.

Strati, Blood Advances, 14 JULY 2020 x VOLUME 4, NUMBER 13

IL-1 IN METABOLIC & CV DISEASE

ΑΝΟΣΟΠΑΡΕΜΒΑΣΗ ΚΑΙ ΠΑΧΥΣΑΡΚΙΑ

Adipose Tissue Immunomodulation: A Novel Therapeutic Approach in Cardiovascular and Metabolic Diseases

Adipokine Profile Dysregulation

Adiponectin

C1q/TNF-related proteins (CTRPs)

Omentin

SFRP5

Leptin

Resistin

Visfatin

Visfatin OR pre-B cell colony-enhancing factor (PBEF)

LCN2 and RBP4

METABOLIC REGULATION AND ADAPTATION OF TISSUE RESIDENT AND INFILTRATING MYELOID CELLS

Macrophages

Dendritic Cells

Neutrophils

Eosinophils

Mast Cells

METABOLIC REGULATION AND ADAPTATION OF TISSUE RESIDENT AND INFILTRATING LYMPHOID CELLS

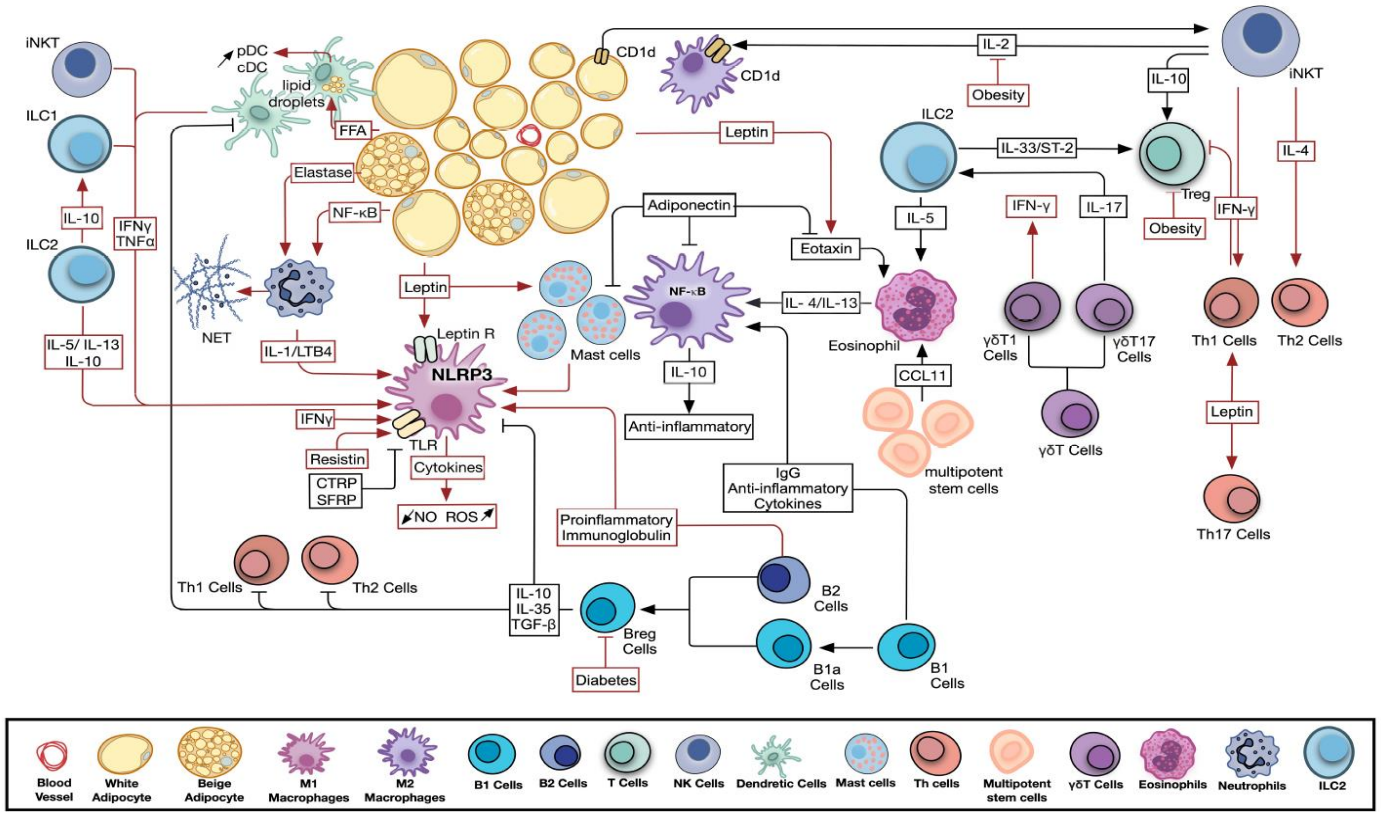
T Cells
- abT Cells
- Regulatory T Cells
- gdT Cells
- iNKT Cells

Innate Lymphoid Cells
- Adipose Tissue ILC1s and NK Cells
- Adipose Tissue ILC2s

B Cells

AlZaim I, Front. Cardiovasc. Med. 2020, 7:602088

Al Zaim I, Front.Cardiovasc.Med.2020,7



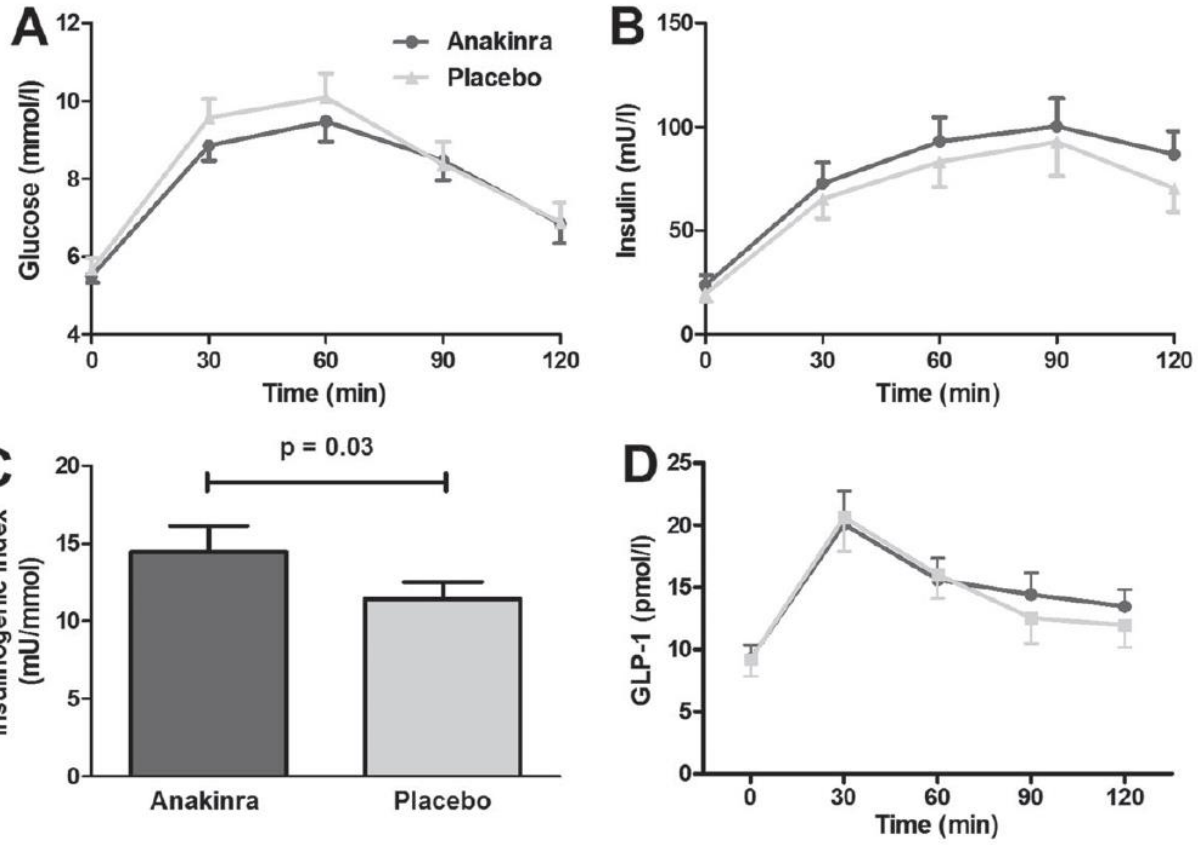
NEW AVENUES FOR ADIPOSE TISSUE IMMUNOMODULATION IN METABOLIC DISORDERS AND CARDIOVASCULAR DISEASES

The antagonism of IL-1R improved IR in T1D patients and DIO mice and in patients with impaired glucose tolerance . One study however highlighted the importance of combining IL-1R antagonism treatment with proper dieting for the treatment of obesity .

Osborn O, Cytokine. (2008) 44:141–8
Van Asseldonk EJP, Clin Immunol. (2015) 160:155–62
Van Poppel PCDiabetes Obes Metab. (2014) 16:1269–73

ANAKINRA and DIABETES

The interleukin-1 receptor antagonist anakinra improves first-phase insulin secretion and insulinogenic index in subjects with impaired glucose tolerance



The main finding of this study is that 4weeks of anakinra treatment improves the insulinogenic index and augments the **first-phase insulin secretion**.
These observations suggest that **anakinra can improve β-cell function**.
However, second-phase insulin secretion, insulin response after arginine and the maximal insulin concentration were not influenced by anakinra

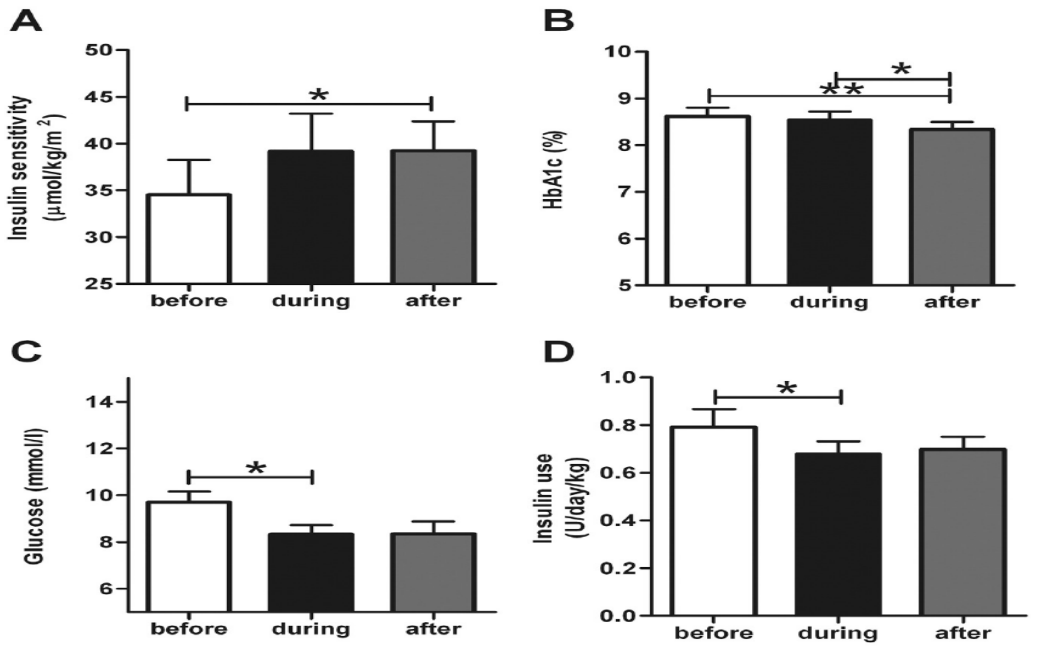
Van Popel ,Diabetes, Obesity and Metabolism 16: 1269–1273, 2014

ANAKINRA and DIABETES

One week treatment with the IL-1 receptor antagonist anakinra leads to a sustained improvement in insulin sensitivity in insulin resistant patients with type 1 diabetes mellitus

Edwin J.P. van Asseldonk[a], Pleun C.M. van Poppel[a], Dov B. Ballak[a], Rinke Stienstra[a,b,*], Mihai G. Netea[a], Cees J. Tack[a]

In conclusion, one week of treatment with anakinra improves insulin sensitivity in patients with 34 type 1 diabetes



Clinical Immunology 2015

Interleukin-1–Receptor Antagonist in Type 2 Diabetes Mellitus

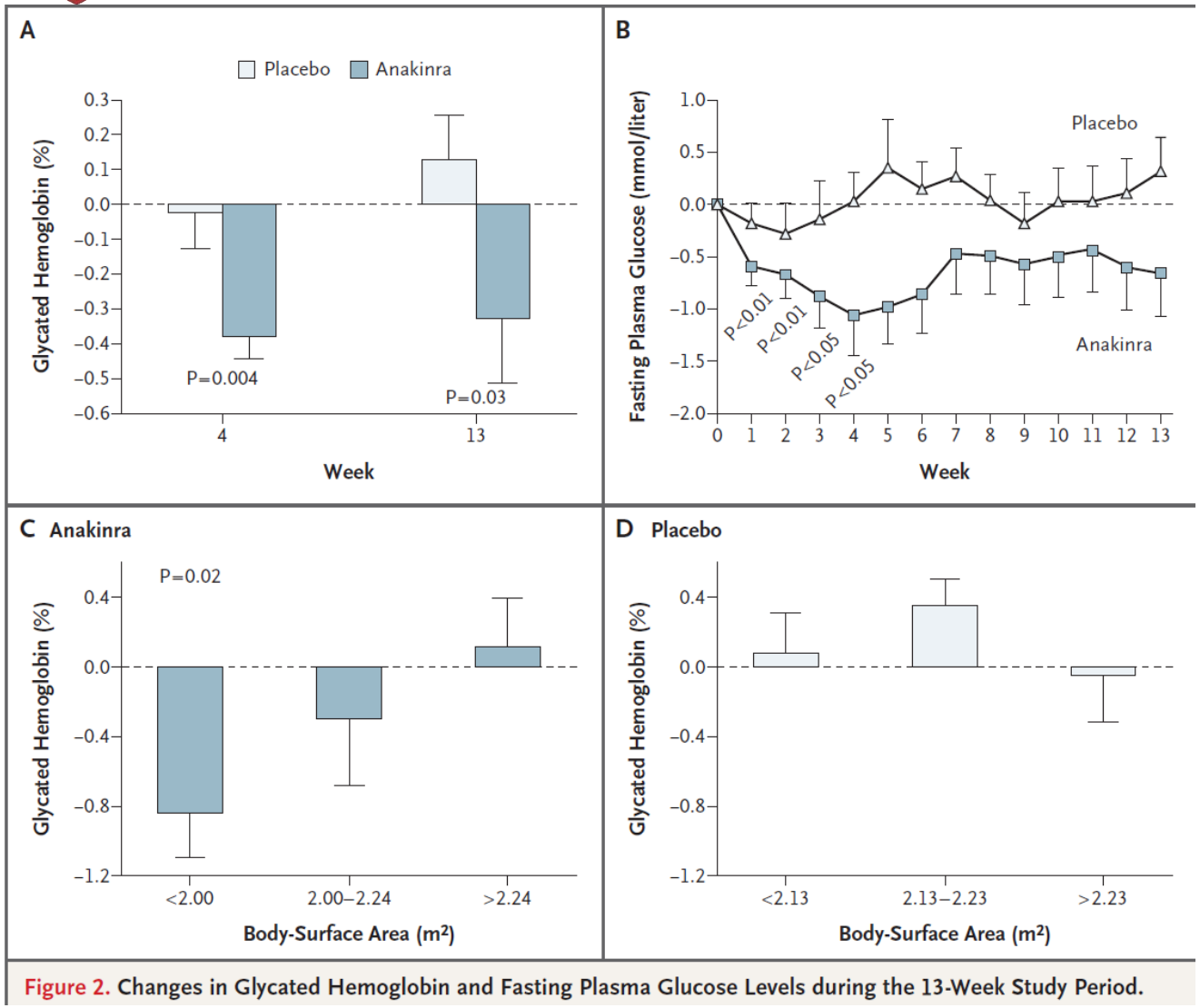


Figure 2. Changes in Glycated Hemoglobin and Fasting Plasma Glucose Levels during the 13-Week Study Period.

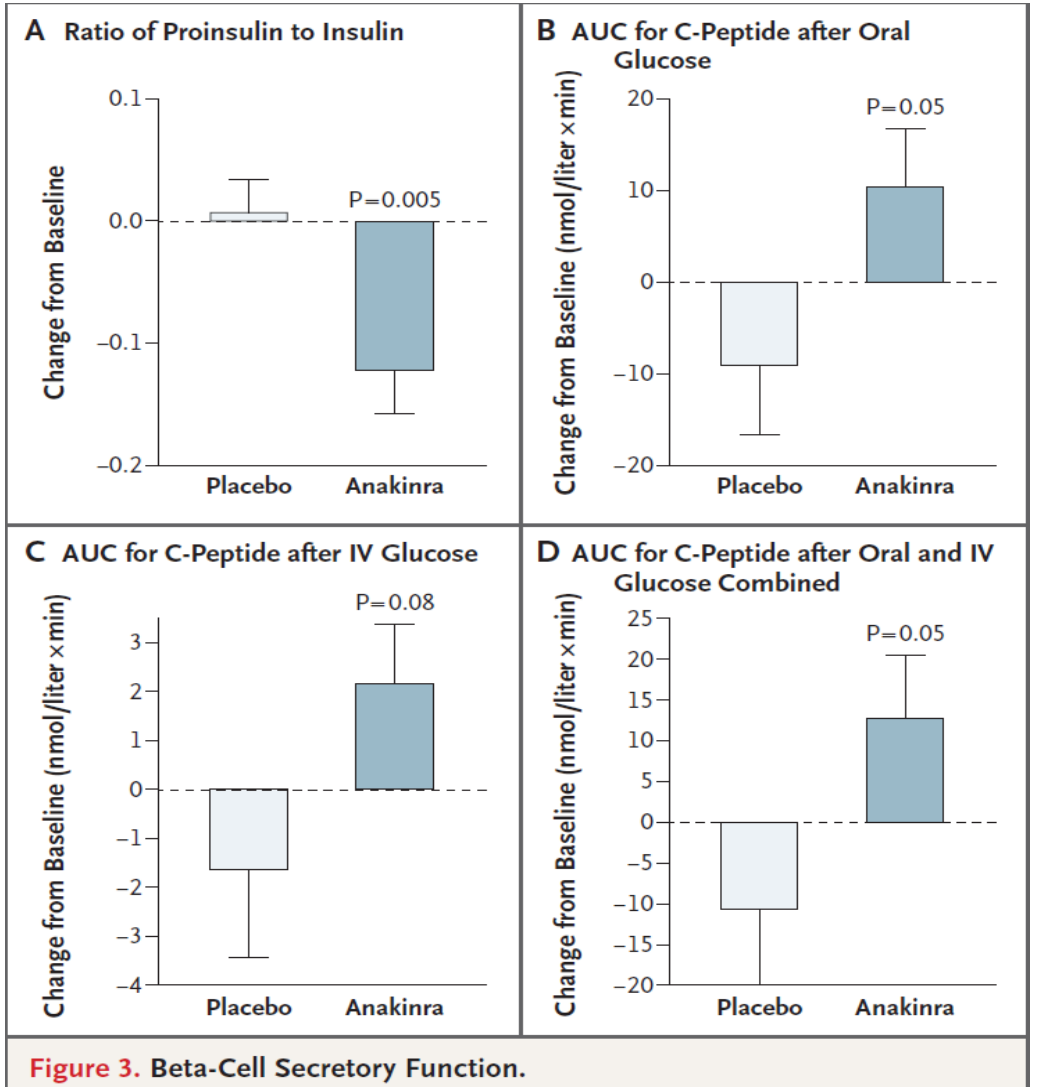


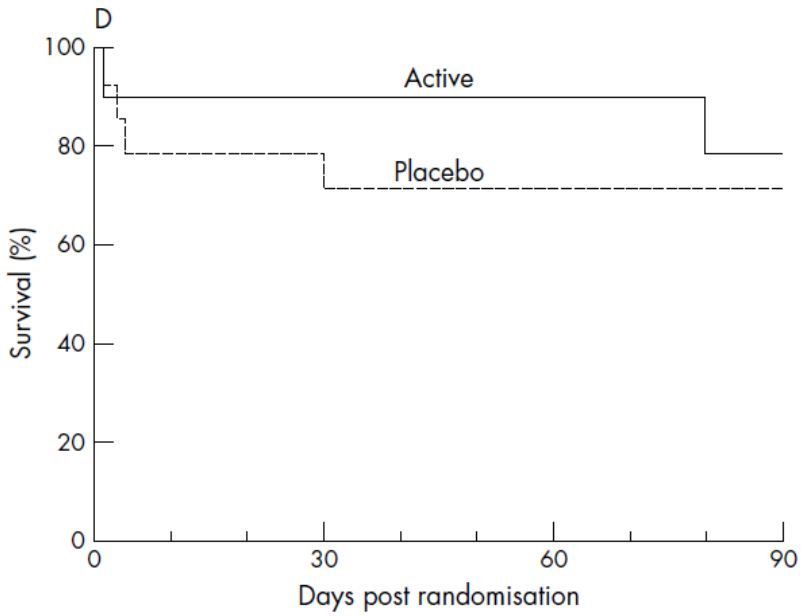
Figure 3. Beta-Cell Secretory Function.

Larsen, N Engl J Med 2007;356:1517-26

A randomised phase II study of interleukin-1 receptor antagonist in acute stroke patients

H C A Emsley, C J Smith, R F Georgiou, A Vail, S J Hopkins, N J Rothwell, P J Tyrrell, for the IL-1ra in Acute Stroke Investigators

STROKE



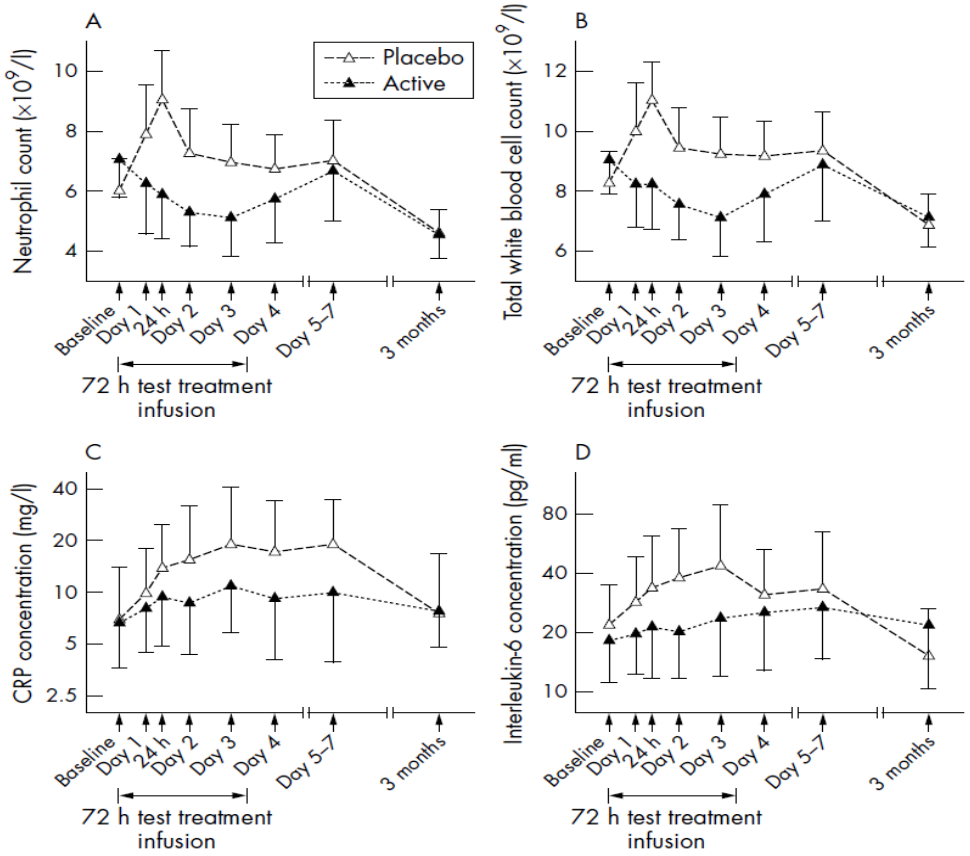


Figure 3 Clinical outcome in patients with cortical infarcts. (A) Boxplot of NIHSS score (boxes denote medians and interquartile ranges; whiskers denote 5th and 95th centiles); (B) Barthel index at 3 months; (C) modified Rankin scale at 3 months; (D) Kaplan-Meier survival curves showing cumulative survival (%) to 3 months by treatment group.

Conclusions: These data suggest that rhIL-1ra is safe and well tolerated in acute stroke. In addition, rhIL-1ra exhibited biological activity that is relevant to the pathophysiology and clinical outcome of ischaemic stroke. Our findings identify rhIL-1ra as a potential new therapeutic agent for acute stroke

J Neurol Neurosurg Psychiatry 2005;76:1366–1372

Ο ΡΟΛΟΣ ΤΗΣ IL-1 ΣΤΗΝ ΑΘΗΡΟΘΡΟΜΒΩΣΗ ΚΑΙ ΤΗΝ ΙΣΧΑΙΜΙΚΗ ΚΑΡΔΙΟΠΑΘΕΙΑ

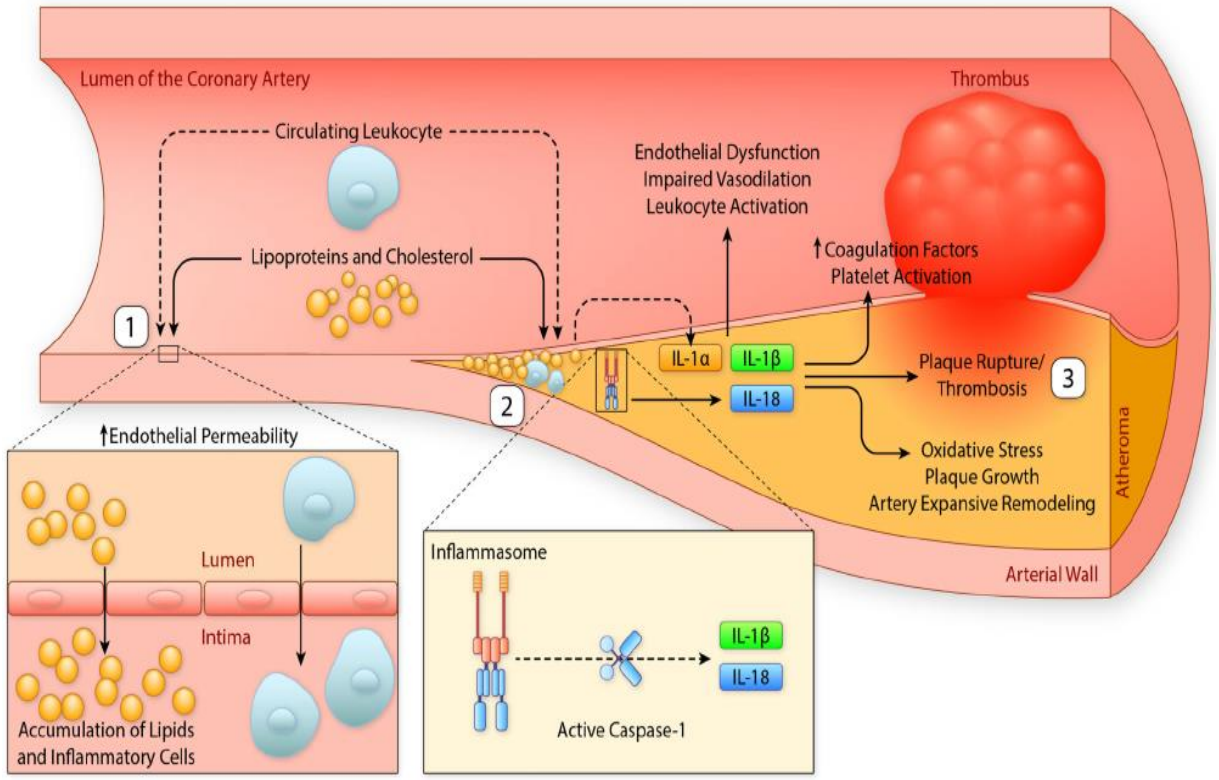
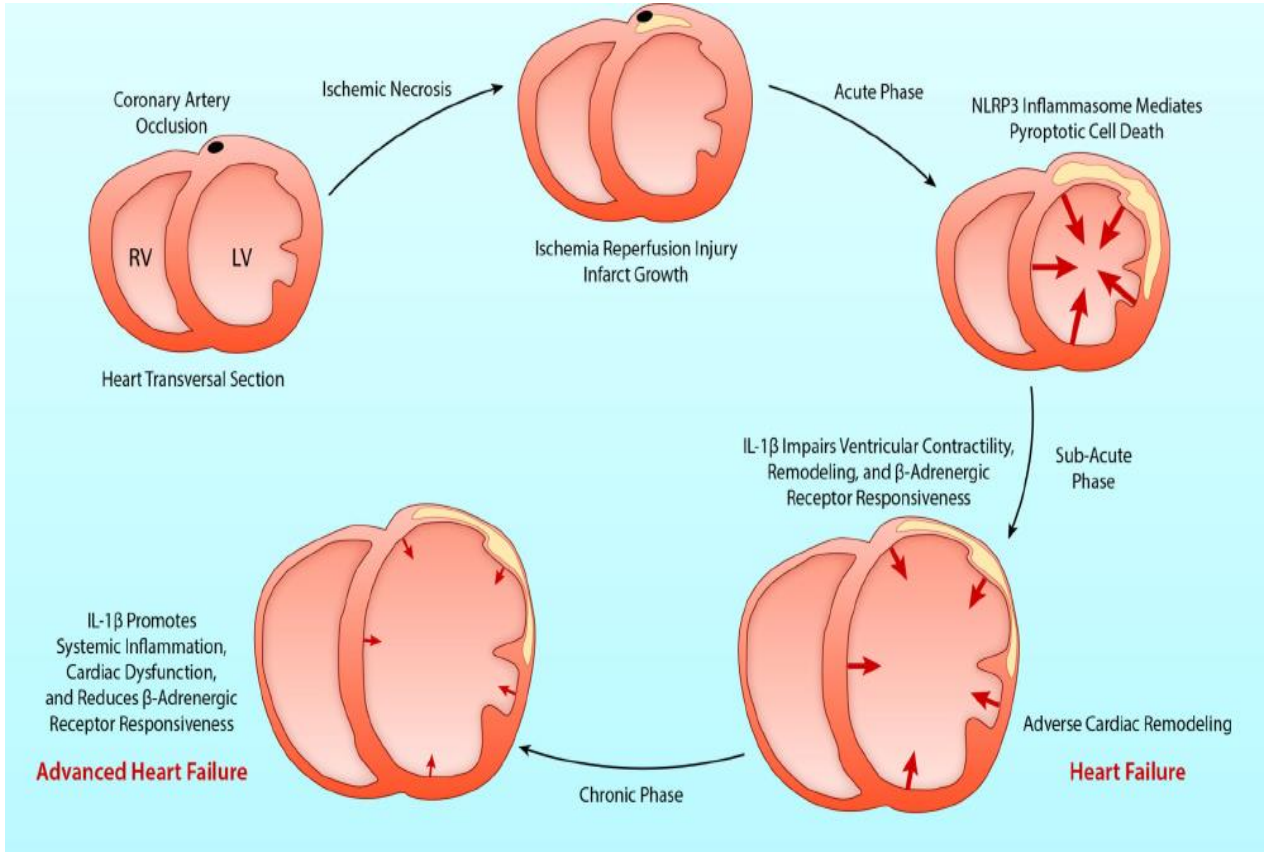


Figure 3. IL-1, inflammasome and atherothrombosis



The anti-atherosclerosis effect of anakinra, a recombinant human interleukin-1 receptor antagonist, in apolipoprotein E knockout mice

Beyond the roles of lipid-lowering therapy with statins, ezetimibe, and PCSK-9 inhibitor, the effective **inhibition of chronic inflammation** may be an important component of anti-atherosclerosis treatment.

Interleukin (IL)-1β is an important mediator of inflammatory responses, driving the expression of mediators such as COX-2, IL-1, IL-6, IL-12, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1, and the (TNF-α) signaling pathway, which all contribute to the development of vascular remodeling and atherosclerosis .

The inflammasome is an intracellular multiprotein complex that activates a pro-inflammatory cascade in response to signals from microbe-derived pathogen-associated molecular patterns and host cell-generated danger-associated molecular patterns. Notably, intracellular protein NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) forms the NLRP3 inflammasome, which mediates the effects of IL-1β related to atherosclerosis

Conclusion IL-1 blockade with anakinra significantly reduced atherosclerotic plaque formation in ApoE−/− mice. Also,anakinra reduced expression of inflammatory genes in endothelial cells, smooth muscle cells, and adipocytes and ameliorated processes involved in vascular remodeling.
Anakinra could be a useful component of complementary treatment with standard regimen to reduce the residual CV risk.

Ku et al DOI: https://doi.org/10.21203/rs.3.rs-482370/v1

IL-1 and HEART

Persistent Expression of Cytokine in the Chronic Stage of Viral Myocarditis in Mice

Shioi, Circulation. 1996;94:2930

Effect of IL-1 Blockade with Anakinra on Heart Failure Outcomes in Patients with Anterior versus Non-Anterior STEMI

Journal of Cardiovascular Pharmacology Publish Ahead of Print(February 2022)
DOI:10.1097/FJC.0000000000001240

Interleukin-1 blockade with anakinra and heart failure following ST-segment elevation myocardial infarction: results from a pooled analysis of the VCUART clinical trials

…IL-1 blockade with anakinra for 14 days in patients with STEMI reduces the incidence of new-onset HF or hospitalization for HF at 1 year following STEMI

Abbate , European Heart Journal - Cardiovascular Pharmacotherapy, 2022, 8; 5: 503–510

IL-1 Blockade in Patients With Heart Failure With Preserved Ejection Fraction: Results From DHART2

CONCLUSIONS: Treatment with anakinra for 12 weeks failed to improve peak Vo2 and VE/Vco2 slope in a group of obese heart failure with preserved ejection fraction patients.

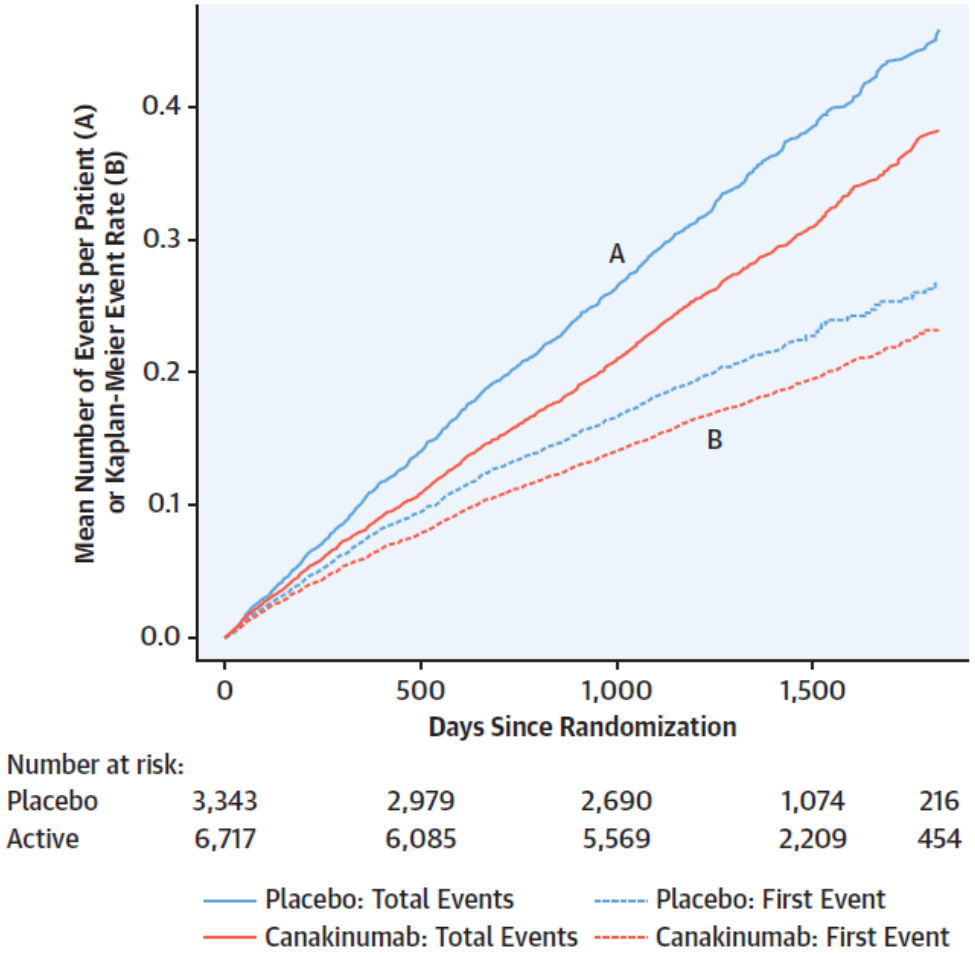
Van Tassell, Circ Heart Fail. 2018 August ; 11(8):

Inhibition of Interleukin-1β and Reduction in Atherothrombotic Cardiovascular Events in the CANTOS Trial

CONCLUSIONS Anti-inflammatory therapy with canakinumab significantly reduced the total number of cardiovascular events in patients with prior MI and evidence of residual inflammatory risk.

(Cardiovascular Risk ReductionStudy [Reduction in Recurrent Major CV Disease Events] (CANTOS); NCT01327846

CENTRAL ILLUSTRATION Time to the First Serious Cardiovascular Event and the Total (First and Subsequent) Serious Cardiovascular Events Over Time in the CANTOS Study



Everett, J Am Coll Cardiol 2020;76

ARAMIS

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ClinicalTrials.gov

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Save this study

Anakinra Versus Placebo for the Treatment of Acute MyocarditIS (ARAMIS)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03018834

Recruitment Status : Completed
First Posted : January 12, 2017
Last Update Posted : June 15, 2022

Sponsor:
Assistance Publique - Hôpitaux de Paris

Information provided by (Responsible Party):
Assistance Publique - Hôpitaux de Paris

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Go to

Brief Summary:

ANAKINRA & HEART

TABLE 3 | Anakinra for the heart.

↓ Inflammation in acute myocardial infarction
↑ Exercise performance in heart failure
↑ Oxygen consumption in heart failure
↓ Systemic inflammation in heart failure
↓ Hospitalizations for recurrent acute heart failure
↓ Pain and inflammation in recurrent idiopathic pericarditis
↑ Function in acute myocarditis and heart failure
↑ Exercise tolerance in heart failure associated with rheumatoid arthritis

Cavalli G and Dinarello CA (2018) Front. Pharmacol. 9:1157

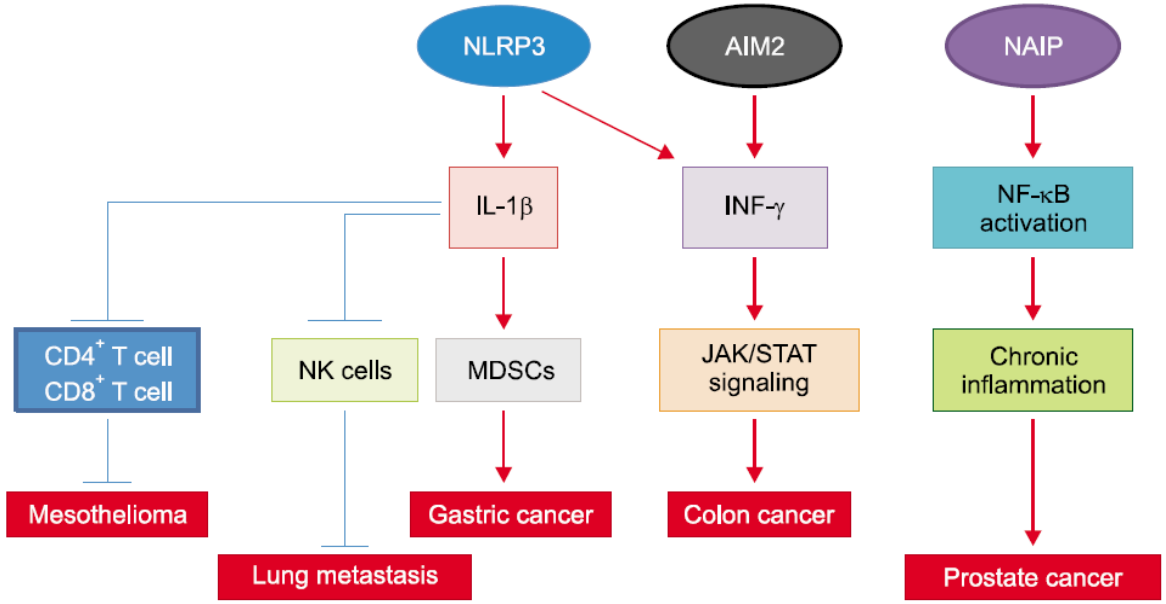
ANAKINRA IN CANCER

Safety and immunologic activity of anakinra in HER2-negative metastatic breast cancer (MBC).

Meeting Abstract | 2016 ASCO Annual Meeting I

DOI: 10.1200/JCO.2016.34.15_suppl.e14565 Journal of Clinical Oncology - published online before print May 20, 2016

Inflammasome as a Therapeutic Target for Cancer Prevention and Treatment



Huyen Trang Ha Thi, J Cancer Prev 2017;22:62-73)

Fluorouracil and bevacizumab plus anakinra for patients with metastatic colorectal cancer refractory to standard therapies (IRAFU): a single-arm phase 2 study

ABSTRACT

In preclinical models, IL-1β inhibition could enhance the efficacy of fluorouracil (5-FU). In this phase 2 study, we assessed the activity and safety of 5-FU plus bevacizumab and anakinra (an IL-1β and α inhibitor) in patients with metastatic colorectal (mCRC) refractory to chemotherapy and anti-angiogenic therapy.

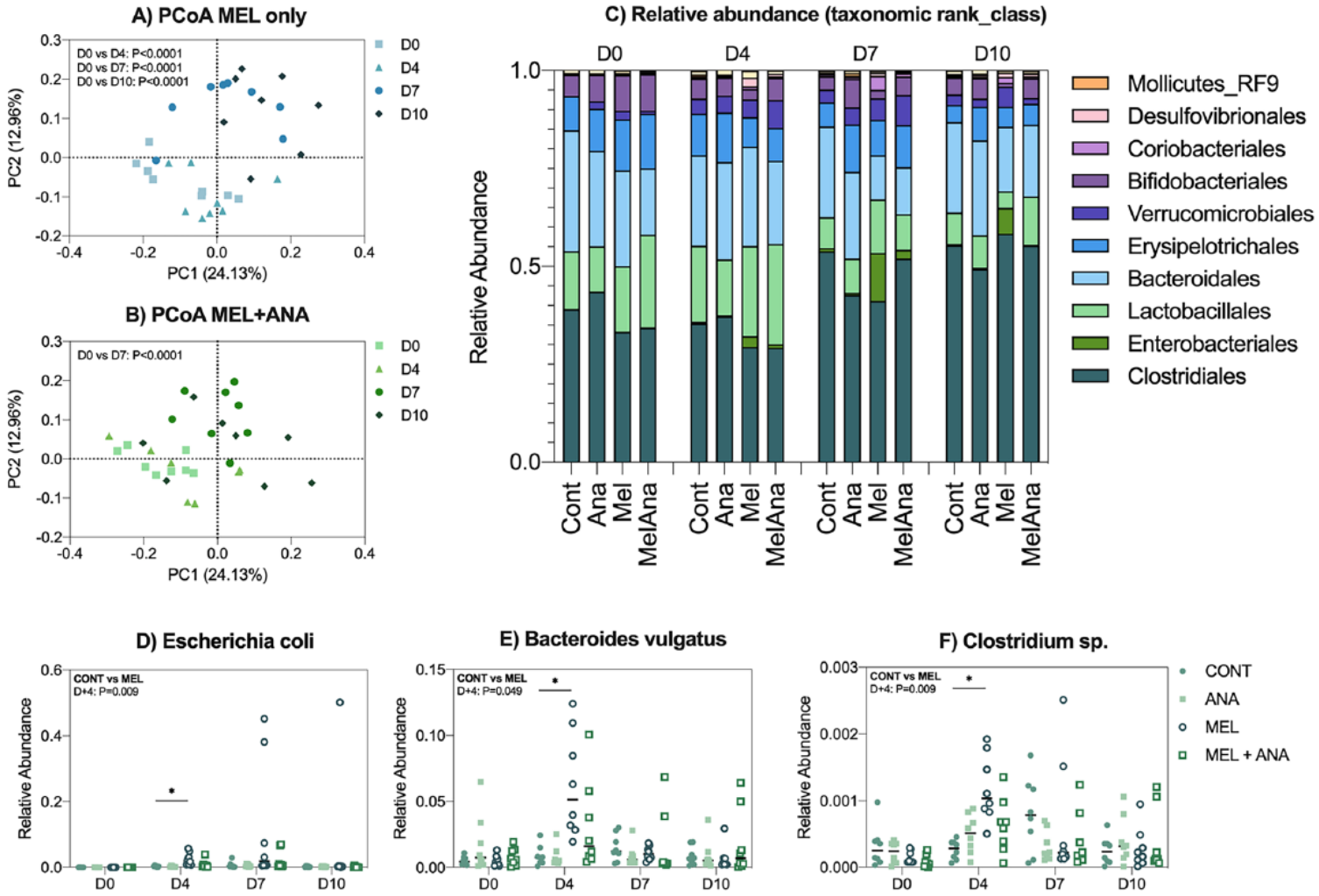
Eligible patients had unresectable mCRC; were refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy, and anti-EGFR therapy (for tumors with wild-type *KRAS*). Patients were treated with a simplified acid folinic plus 5-FU regimen and bevacizumab (5 mg/kg) both administered by intravenous infusion for 30 min every 2 weeks. Anakinra (100 mg) was injected subcutaneously once daily. The primary endpoint was the 2-month response rate determined upon CHOI criteria.

Thirty two patients with metastatic colorectal cancer were enrolled. Five patients demonstrated response (Choi criteria) and 22 patients had stable disease as the best 2-month overall response. Median progression-free and overall survival were 5.4 (95% CI, 3.6–6.6) and 14.5 months (95% CI, 9–20.6) respectively. Twenty patients experienced grade 3 toxicity. No grade 4 or 5 toxicity related to therapy occurred. The most common grade 3 adverse events were neutropenia in 8 (25%) patients, digestive side effects in 7 (21.9%) patients and hypertension in 6 (18.75%) patients. No treatment-related deaths or serious adverse events were reported.5-FU plus bevacizumab and anakinra has promising activity and a manageable safety profile, suggesting that this combination might become a potential treatment option for patients with refractory mCRC.

Isambert, OncoImmunology, 2018, 7:9, e1474319

AFFECT-1 Phase IIA trial in Transplanted Myeloma Patients

Supporting the gastrointestinal microenvironment during high-dose chemotherapy and stem cell transplantation by inhibiting IL-1 signaling with anakinra



Wardill, Nature Scientific Reports ,(2022) 12:6803

ANAKINRA IN CGD

Anakinra for Treatment of Liver Abscesses in a Patient with a Novel *CYBB* Variant of Chronic Granulomatous Disease

Caroline To, Journal of Clinical Immunology,2021

Netherlands
The Journal of Medicine

LETTER TO THE EDITOR

Anakinra for the inflammatory complications of chronic granulomatous disease

F.L. van de Veerdonk, M.G. Netea, C.A. Dinarello,J.W.M. van der Meer 2011

IL-1 receptor blockade restores autophagy and reduces inflammation in chronic granulomatous disease in mice and in humans

de Luca et al. PNAS March 4, 2014 vol. 111 no. 9

SARCOIDOSIS

PROTOCOL Open Access

Interleukin-1 blockade in cardiac sarcoidosis: study design of the multimodality assessment of granulomas in cardiac sarcoidosis: Anakinra Randomized Trial (MAGiC-ART)

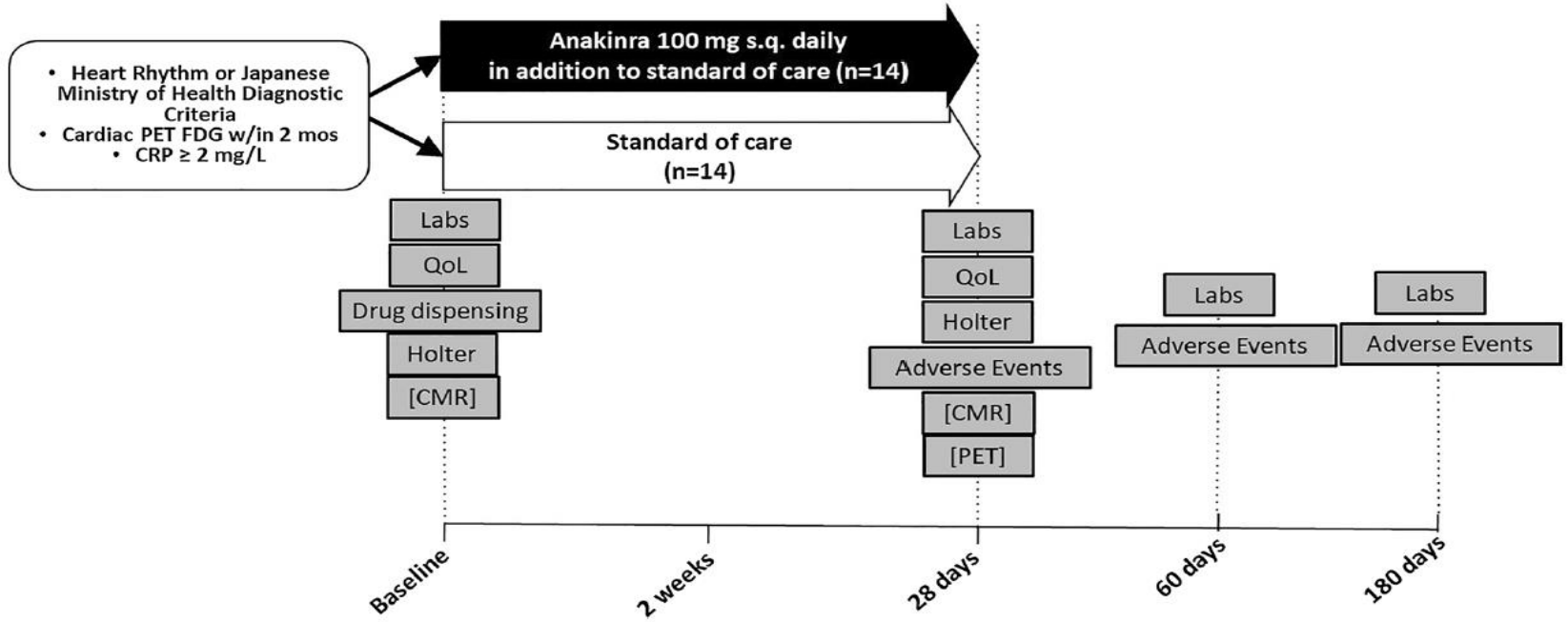


Fig. 1 Design of the Multimodality Assessment of Granulomas in Cardiac Sarcoidosis—Anakinra Randomized Trial (MAGiC-ART). The overall study design is represented as a schematic. Abbreviations: CMR, cardiac magnetic resonance; CRP, C-reactive protein; HRS, Heart Rhythm Society; PET, positron emission tomography; QoL, quality of life. Procedures shown in brackets are additional testing done as part of the VCU Imaging Sub-study

Kron et al. J Transl Med (2021) 19:460

SECONDARY AMYLOIDOSIS
Causes of secondary, AA, amyloidosis

Chronic Infections
Tuberculosis
Leprosy
Whipple Disease
Osteomyelitis
Chronic pyelonephritis
Subacute bacterial endocarditis
Chronic cutaneous ulcers

Inflammatory Arthritis
Adult-onset Still disease
Ankylosing spondylitis
Juvenile idiopathic arthritis
Psoriatic arthropathy
Reiter syndrome
Rheumatoid arthritis
Gout

Conditions Predisposing to Chronic Infections
Cystic fibrosis
Bronchiectasis
Kartagener syndrome
Epidermolysis bullosa
Injected drug abuse
Jejuno-ileal bypass
Paraplegia
Sickle cell anemia
Immunodeficiency
Common variable immunodeficiency
Cyclic neutropenia
Hyperimmunoglobulin M syndrome
Hypogammaglobulinemia
Sex-linked agammaglobulinemia
Human immunodeficiency virus/AIDS

Systemic Vasculitis
ANCA associated vasculitis
Behcet disease
Giant cell arteritis
Polyarteritis nodosa
Polymyalgia rheumatica
Systemic lupus erythematosus
Takayasu arteritis

Periodic Fevers
Cryopyrin-associated periodic fever syndrome
Familial Mediterranean fever
Mevalonate kinase deficiency
Tumor necrosis factor receptor associated periodic syndrome
Inflammatory Bowel Disease

Neoplasia
Adenocarcinoma
Basal cell carcinoma
Carcinoid tumor
Castleman disease
Gastrointestinal stromal tumor
Hairy cell leukemia
Hepatic adenoma
Hodgkin disease
Mesothelioma
Renal cell carcinoma
Sarcoma

Others
Atrial myxoma, Inflammatory abdominal aortic aneurism, Retroperitoneal fibrosis
SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome, Sarcoidosis
Sinus histiocytosis with massive lymphadenopathy

Papa, Rheum Dis Clin North Am . 2018 Nov;44(4):585-603

Empirical use of anakinra in AA amyloidosis of uncertain aetiology

T Lane*, DM Rowczenio, JA Gilbertson, JD Gillmore, AD Wechalekar, PN Hawkins, HJ Lachmann

From 8th International Congress of Familial Mediterranean Fever and Systemic Autoinflammatory Diseases
Dresden, Germany. 30 September - 3 October 2015

Conclusion

……AA amyloidosis is a potentially reversible cause of renal failure.
A therapeutic trial of anakinra is worth trying as it is potentially completely effective and has a better safety profile than high dose corticosteroids, other anticytokine or immunosuppressive drugs.

Lane et al. Pediatric Rheumatology 2015, 13(Suppl 1):O70

ΑΣΦΑΛΕΙΑ

As with all biologic agents, an increase in infection frequency has been reported for anakinra. Nevertheless, in comparison to other biologic agents, anakinra has an unparalleled safety benefit deriving from short half-life and effect duration, and has demonstrated a remarkable record of safety
Fleischmann et al., 2006; Mertens and Singh, 2009)

In humans, anakinra has been administered to patients with active infections (Hennig et al., 2010; van de Veerdonk et al., 2011), and in over 2000 patients in trials of sepsis and septic shock without any increase in mortality despite exceedingly high dosing (30-fold higher than the current approved dose of 100 mg/day; Dinarello et al., 2012

Subcutaneous administrations of anakinra often cause injection site reactions

neutrophil levels occasionally fall below the normal range, only to rise rapidly upon cessation of treatment (Cavalli and Dinarello, 2015)

Long-term efficacy and safety of anakinra in a patient with Behçet's disease and concomitant tuberculosis infection

Unlike anti-TNFa treatment, IL-1 inhibition has shown a good safety profile regarding the risk of severe infections, particularly in relation to tuberculosis (TB) reactivation.

Emmi, International Journal of Dermatology 2016

BMJ Open

Trial summary and protocol for a phase II randomised placebo-controlled double-blinded trial of Interleukin 1 blockade in Acute Severe Colitis: the IASO trial

Methods and analysis IASO is a phase II, multicentre, two-arm (parallel group), randomised (1:1), placebo-controlled, double-blinded trial of short-duration anakinra in ASUC. Its primary outcome will be the incidence of medical (eg, infliximab/ciclosporin) or surgical rescue therapy (colectomy) within 10 days following the commencement of intravenous corticosteroid therapy. Secondary outcomes will include disease activity, time to clinical response, time to rescue therapy, colectomy incidence by day 98 post intravenous corticosteroids and safety. The trial aims to recruit 214 patients across 20 sites in the UK.

Thomas MG, et al. BMJ Open 2019;9:e023765

ΣΥΜΠΕΡΑΣΜΑΤΑ

Η IL-1 έχει κυρίαρχο ρόλο στην ενεργοποίηση και διατήρηση της φλεγμονής

Με τη δράση της σε πολλούς ιστούς και όργανα συμμετέχει στην παθοφυσιολογία πλείστων παθήσεων

Η αναστολή της τεκμηριωμένα συμβάλλει στην αντιμετώπιση πολλών φλεγμονοδών νοσημάτων

Η πρόσφατη αδειοδότησή του ανασυνδυασμένου αναστολέα της IL-1 στην αντιμετώπιση της COVID-19 απέδειξε ότι η χρήση αυτών των αγωγών μπορεί να συμβάλλει στο μέλλον στην αντιμετώπιση νοσημάτων που η IL-1 διαδραματίζει σημαντικό ρόλο.

ΣΑΣ ΕΥΧΑΡΙΣΤΩ