

Supplementary Information

Scoping review on the use of interleukin 1-pathway targeting drugs in DIRA and DITRA diseases

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1. Supplementary Methods

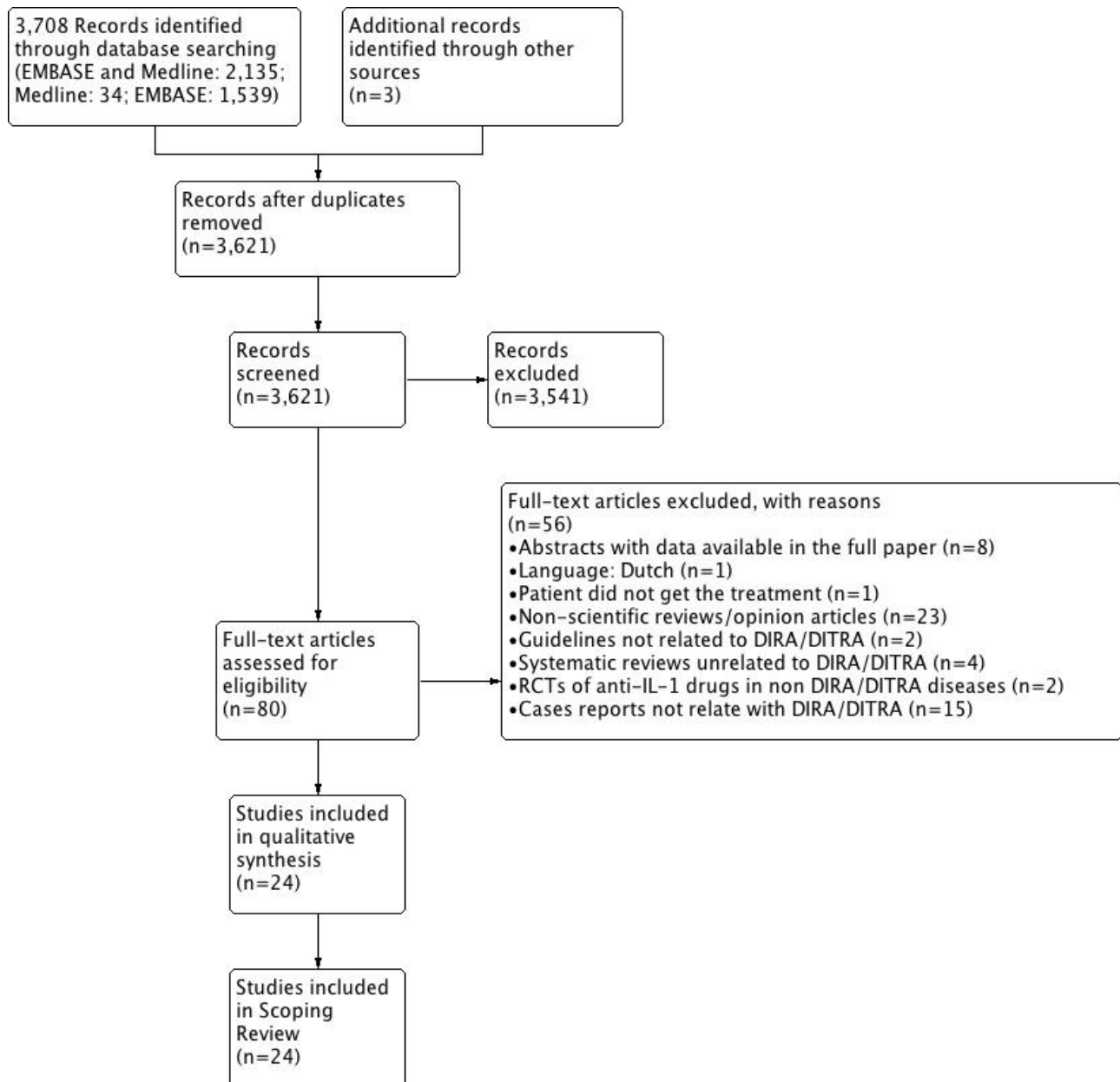
This is the strategy followed for the second databases' search.

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((treatment) AND (('interleukin 1beta') OR ('interleukin 1'))) AND ('skin disease') OR (('canakinumab') OR ('anakinra') OR ('rilonacept') OR (mabpl)) AND (('candle syndrome'/exp OR 'candle syndrome') OR (neutrophilic AND urticarial AND dermatosis) OR (undifferentiated AND autoinflammatory AND syndromes) OR (autoinflammatory AND skin AND bone AND disease) OR ('cryopyrin associated' AND periodic AND syndromes) OR (aseptic AND abscess AND syndrome) OR (acute AND febrile AND neutrophilic AND dermatosis) OR ('pyrin associated' AND autoinflammation AND with AND neutrophilic AND dermatosis) OR (deficiency AND of AND 'interleukin 1' AND receptor AND antagonist) OR (nonbacterial AND osteomyelitis AND associated AND diseases) OR (papa AND syndrome) OR (neutrophilic AND dermatoses AND in AND 'adult onset' AND autoinflammatory AND syndromes) OR (majeed AND syndrome) OR (sapho AND syndrome) OR (chronic AND recurrent AND multifocal AND osteomyelitis) OR (amicrobial AND pustulosis AND of AND the AND skin AND fold) OR (refractory AND aseptic AND abscesses AND syndrome) OR ('blau syndrome') OR (chronic AND atypical AND neutrophilic AND dermatitis AND with AND lipodystrophy AND elevated AND temperature AND syndrome) OR ('neonatal onset' AND multisystem AND inflammatory AND disease) OR (chronic AND infantile AND neurologic, AND cutaneous, AND arthritis) OR (still AND disease) OR ('pash syndrome') OR ('macrophage activation syndrome') OR (neutrophilic AND panniculitis) OR ('tumor necrosis factor receptor associated periodic syndrome') OR ('pfapa syndrome') OR (autoinflammatory AND disease AND associated AND with AND mutations) OR (hidradenitis AND suppurativa) OR ('suppurative hidradenitis') OR ('psoriasis') OR ('atopic dermatitis') OR (pyoderma AND gangrenous) OR ('pyoderma gangrenosum') OR ('skin allergy') OR ('acne') OR (pustular AND psoriasis) OR (dissecting AND cellulitis AND of AND the AND scalp) OR (childhood AND pustular AND dermatosis) OR (refractory AND 'anti mda5' AND clinically AND amyopathic AND dermatomyopathy) OR (autoimmune AND bullous AND dermatoses) OR (acrodermatitis AND continua AND of AND hallopeau) OR ('melanoma') OR ('schnitzler syndrome')
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OR ('erdheim chester' AND disease) OR (neck AND squamous AND cell AND carcinoma) OR (squamous AND cell AND carcinoma) OR ('langerhans cell histiocytosis') OR ('skin cancer') OR ('multicentric reticulohistiocytosis') OR ('poems syndrome') OR ('erythema nodosum') OR (prurito) OR (pigmentary AND hypertrichosis AND nonautoimmune AND 'insulin dependent' AND diabetes AND mellitus AND phid AND syndrome) OR (systemic AND sclerosis AND morphoea) OR (autosomal AND recessive AND congenital AND ichthyoses) OR ('recessive dystrophic epidermolysis bullosa') OR (chronic AND ulcers) OR ('pemphigus vulgaris') OR ('erythema elevatum diutinum') OR ('xanthelasma palpebrarum') OR ('netherton disease') OR (acute AND radiation AND dermatitis) OR (aicardi AND goutieres AND syndrome) OR ('granulomatous skin disease') OR ('scleroderma') OR ('lichen sclerosus et atrophicus') OR ('pemphigus foliaceus') OR ('ocular rosacea') OR ('amyloidosis') OR ('lupus erythematosus') OR ('sjoegren syndrome') OR (still AND disease) OR ('familial mediterranean fever') OR (cryopirin AND associated AND inflammatory AND syndrome) OR ('muckle wells')) OR ('tumor necrosis factor receptor associated periodic syndrome')) AND ('case report'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'drug dose comparison'/de OR 'human'/de OR 'human cell'/de OR 'human tissue'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'observational study'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 3 clinical trial (topic)'/de OR 'practice guideline'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'retrospective study'/de OR 'systematic review'/de

Supplementary figures.

Figure 1.



Supplementary tables.

Table S1. Main features related with the included articles about DIRA.

I D	Title	Journal	Journal speciality	Year	Authors	Nº authors	Type of publication	Country	Language
32	A case report of a novel compound heterozygous mutation in a brazilian patient with deficiency of IL1RA (DIRA)	Journal of Clinical Immunology (2017) 37:1 Supplement 1 (S19).	Immunology	2017	Mendoni LO, et al.	10	Abstract	Brazil	English
24	Deficiency of interleukin-1 receptor antagonist (DIRA): report of the first indian patient and a novel deletion affecting IL1RN	Journal of Clinical Immunology (2017) 37:5 (445-451).	Immunology	2017	Mendonca LO, et al.	12	Full paper	Brazil	English
33	Turkish DIRA patient with novel IL1RN gene mutation	Pediatric Rheumatology (2015) 13 SUPPL. 1 (256DUMMY).	Rheumatology	2015	Berdeli A, et al.	5	Abstract	Turkey	English
34	Interleukin-1 receptor antagonist deficiency with a novel mutation; late onset and successful treatment with canakinumab: a case report	Journal of Medical Case Reports (2015).	General medicine	2015	Ulusoy E, et al.	6	Full paper	Turkey	English
31	Deficiency of interleukin-1 receptor antagonist responsive to anakinra	Pediatric Dermatology (2013) 30:6 (758-760).	Dermatology	2013	Schnellbacher C, et al.	7	Full paper	USA	English
18	IL-1 inhibition in a patient with polymorphism in the interleukin 1-receptor type 1 gene and clinical phenotype of CRMO/DIRA	Annals of the Rheumatic Disease (2013) 71 SUPPL. 3.	Rheumatology	2013	Zimmer C, et al.	6	Abstract	Germany	English
36	Safety and efficacy of anakinra in patients with deficiency of interleukin-1 receptor antagonist	Arthritis and Rheumatism (2012) 64 SUPPL. 10 (S861).	Rheumatology	2012	Montealegre GA, et al.	17	Abstract	USA	English
30	Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis	Archives of Dermatology (2012) 148:6 (747-752).	Dermatology	2012	Minkis K, et al.	8	full paper	USA	English
37	Deficiency of interleukin-1-receptor antagonist syndrome: a rare auto-inflammatory condition that mimics multiple classic radiographic findings	Pediatric Radiology (2012) 42:4 (495-498).	Radiology	2012	Thacker PG, et al.	3	Full paper	USA	English
29	Chronic cutaneous pustulosis due to a 175kb deletion on chromosome 2q13: excellent response to anakinra	Archives of Dermatology (2012) 148:3 (301-304).	Dermatology	2012	Brau-Javier CN, et al.	3	Full paper	Puerto Rico	English
38	A novel mutation of IL1RN in the deficiency of interleukin-1 receptor antagonist syndrome: description of two unrelated cases from Brazil	Arthritis and Rheumatism (2011) 63:12 (4007-4017).	Rheumatology	2011	Jesus AA, et al.	18	Full paper	Brazil	English
39	The first reported case of compound heterozygous IL1RN mutations causing deficiency of the interleukin-1 receptor antagonist	Arthritis and Rheumatism (2011) 63:12 (4018-4022).	Rheumatology	2011	Stenerson M, et al.	6	Full paper	USA	English
1	An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist	New England Journal of Medicine (2009) 360:23 (2426-2437).	General medicine	2009	Aksentjevich I, et al.	45	Full paper	USA	English
5	An autoinflammatory disease due to homozygous deletion of the IL1RN Locus	N Engl J Med. 2009 June 4; 360(23): 2438-2444.	General medicine	2009	Reddy S, et al.	8	Full paper	USA	English
43	Rilonacet maintains long-term inflammatory remission in patients with deficiency of the IL-1 receptor antagonist	JCI Insight. 2017 Aug 17;2(16). pii: 94838.	General medicine	2017	Garg, et al.	11	Full paper	USA	English

Table S2. Main features related with the included articles about DIRA (cont.).

ID	Type of study	Subtype	Anti IL-1 drugs	Patients	Uni/multicentric (n° centers)	n° affiliations	Specialities involved	A priori design	Registered protocol	Funding	Funding type	CoI
32	Observational	Case report	Anakinra / Canakinumab	n=1	Multicentric (n=2)	3	Immunology/Allergy Genetics	No	No	NA	NA	NA
24	Observational	Case report	Anakinra	n=1	Multicentric (n=2)	6	Rheumatology Pediatrics Genetics Immunology/Allergy	Yes (NCT02974595)	Yes	Intramural Research Program of the NIH, NIAID, NIAMS, and NHGRI.	Public	Yes (Novartis)
33	Observational	Case report	Anakinra	n=1	Unicentric	1	Pediatrics	No	No	NA	NA	NA
34	Observational	Case report	Canakinumab	n=1	Multicentric (n=2)	2	Pediatrics Genetics	No	No	NA	NA	No
31	Observational	Case report	Anakinra	n=1	Multicentric (n=3)	5	Pediatrics Dermatology Rheumatology Genetics	No	No	NA	NA	NA
18	Observational	Case report	Anakinra	n=1	Multicentric (n=3)	5	Pediatrics Rheumatology Genetics	No	No	NA	NA	No
36	Observational	Case report	Anakinra	n=5	Multicentric (n=8)	13	Pediatrics Dermatology Rheumatology Genetics Immunology / Allergy Radiology	No	No	NA	NA	No
30	Observational	Case report	Anakinra	n=1	Multicentric (n=2)	7	Pediatrics Dermatology Rheumatology Genetics Immunology / Allergy	No	No	NIAMS/NHGRI	Public	No
37	Observational	Case report	Anakinra / Canakinumab	n=1	Unicentric	1	Radiology	No	No	NA	NA	NA
29	Observational	Case report	Anakinra	n=1	Multicentric (n=2)	2	Dermatology Genetics University	No	No	No	No	No
38	Observational	Case report	Anakinra	n=2	Multicentric (n=6)	6	Dermatology Genetics Pharmaceutical industry	No	No	ANGEM Conselho Nacional de Desenvolvimento Científico e Tecnológico-CNPq Fundação de Amparo à Pesquisa do Estado de São Paulo NIH (through the National Institute of Arthritis and Musculoskeletal and Skin Diseases Intramural Research Program Shafallah Center Foundation, and the Shafallah Medical Genetics Center.	Public / pharmaceutical industry	Yes
39	Observational	Case report	Anakinra	n=1	Multicentric (n=2)	3	Pediatrics Genetic University	No	No	NA	NA	NA

1	Observational	Case series	Anakinra	n=9	Multicentric (n=9)	14	Pediatrics Rheumatology Genetics Immunology / Allergy Radiology General / Internal medicine University	Yes	Yes (NCT00 059748)	NIAMS/NHGRI Children's Miracle Network, and the Peregrine Charities NIH Clinical Research Training program	Public / Private	Yes (La Roche/ Amgen/ Pfizer / Illumina/ Genentech)
5	Observational	Case report	Anakinra	n=1	Unicentric	2	Pediatrics General / Internal medicine University	No	No	National Institute of Allergy and Infectious Diseases (RO1AI078713 and U19AI062627) Research and Education Foundation of the American College of Rheumatology The Children's Hospital of Wisconsin Foundation.	Public	No
43	Intervention	Clinical trial	Rilonacept	n=6	Multicentric (n=6)	8	Pediatrics Rheumatology Immunology / Allergy Radiology University	Yes (NCT018014 49)	Yes	The Intramural Research Program of the NIH, NIAID, and NIAMS.	Public	Yes (Regenero n/ Sobi/ Novartis/ Lilly)

Table S3. Main features related with the included articles about DITRA.

Id	Title	Journal	Journal speciality	Year	Authors	N° authors	Type of publication	Country	Language
19	Juvenile interleukin-36 receptor antagonist deficiency (DITRA) with c.80T>C (p.Leu27Pro) mutation successfully treated with etanercept and acitretin	JAAD Case Reports (2018) 4:2 (192-195).	Dermatology	2018	Cuperus E, et al.	7	Full paper	Holland	English
22	The therapeutic challenge of DITRA syndrome	Pediatric Rheumatology (2017) 15 Supplement 1.	Rheumatology	2017	Caorsi R, et al.	8	Abstract	Italy	English
21	Response to interleukin (IL)-17 Inhibition in an adolescent with severe manifestations of IL-36 receptor antagonist deficiency (DITRA)	JAMA Dermatology (2017) 153:1 (106-108).	Dermatology	2017	Cordero KM, et al.	5	Letter	USA	English
41	Pneumocystis jirovecii pneumonia in a patient with pustular psoriasis with an IL-36RN deficiency treated with infliximab: case report and review of the literature	Australasian Journal of Dermatology (2017) 58:2 (e44-e47).	Dermatology	2017	Podlipnik S, et al.	4	Full paper	Spain	English
20	Combined therapy in 2 cases of pustular generalized psoriasis with IL36RN gene mutations	Pediatric Dermatology (2017) 34 Supplement 2 (S46).	Dermatology	2017	Capusan TM, et al.	10	Abstract	Spain	English
42	Homozygous IL36RN mutation and NSD1 duplication in a patient with severe pustular psoriasis and DITRA-unrelated symptoms	Br J Dermatol. 2015;172: 302-305.	Dermatology	2015	Carapito, et al.	15	Letter	France	English
40	Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations	Br J Dermatol. 2014;170(5):1198-1199.	Dermatology	2014	Tauber M, et al.	5	Letter	Germany	English
44	Generalized pustular psoriasis in infant with heterozygous mutation in the IL36RN gene successfully treated with infliximab	Pediatr Rheumatol Online J. 2014; 12(Suppl 1): P79.	Rheumatology	2014	Glerup, et al.	5	Abstract	Denmark	English
35	First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra	Pediatrics (2013) 132:4 (e1043-e1047).	Pediatrics	2013	Rossi-Semerano L, et al.	6	Full paper	France	English
5	An autoinflammatory disease due to homozygous deletion of the IL1RN Locus	N Engl J Med. 2009 June 4; 360(23): 2438–2444	General medicine	2009	Reddy S, et al.	8	Full paper	USA	English

Table 2. Main features related with the included articles about DITRA (cont.).

ID	Type of study	Subtype	Anti IL-1 drugs	Patients	Uni/multicentric (n° centers)	n° affiliations	Specialities involved	A priori design	Registered protocol	Funding	Funding type	CoI
19	Observational	Case report	Anakinra	n=1	Unicentric	4	Dermatology Pediatrics Genetics	No	No	No	No	No
22	Observational	Case report	Anakinra	n=1	Unicentric	3	Dermatology Pediatrics Genetics	No	No	NA	NA	No
21	Observational	Case report	Anakinra	n=1	Unicentric	1	Rheumatology Dermatology	No	No	No	No	Yes (Novartis/ Abbie/ Pfizer/ Jansen)
41	Observational	Case report	Anakinra	n=1	Multicentric (n=4)	4	Pediatrics	No	No	No	No	Yes (Novartis/ Sobi)
20	Observational	Case report	Anakinra	n=1	Multicentric	2	Dermatology Genetics Pathological Anatomy	No	No	NA	NA	NA
42	Observational	Case report	Anakinra	n=1	Unicentric	2	Dermatology	No	No	NA	NA	NA
40	Observational	Case report	Anakinra	n=1	Unicentric	2	Pediatrics General / Internal medicine University	No	No	National Institute of Allergy and Infectious Diseases (RO1AI078713 and U19AI062627) Research and Education Foundation of the American College of Rheumatology The Children's Hospital of Wisconsin Foundation.	Public	No
44	Observational	Case report	Anakinra	n=1	Multicentric	7	Pediatrics Dermatology Genetics Pathological Anatomy	No	No	Strasbourg High Throughput Next Generation Sequencing facility (GENOMAX) and INSERM UMR_S 1109.	Public	NA
35	Observational	Case report	Anakinra	n=1	Multicentric	3	Pediatrics Dermatology Immunology / Allergy	No	No	NA	No	No