Universidad Católica de Valencia San Vicente Mártir

Facultad de Medicina y Odontología

Grado en Medicina

Trabajo de Fin de Grado

The molecular basis of juvenile idiopathic arthritis and its correlation with other immune mediated diseases

A systematic review

Author

Gemma Clara Meira Blanco

Director

Dr. Ignacio Ventura González

Valencia, April 5th 2023

Abstract

Background: JIA is currently the most common chronic rheumatic disease in children. It is known that it does not consist of a solely identity but a variety of diagnosis. Its underdiagnosis is a barrier that puts stop to prompt treatment and fewer complications of this disease. We now know that other immune mediated disease can coexist on the same patient, making relevant the investigation in this area.

Objective: The main objective of this review is to try and stablish a relationship between Juvenile Idiopathic Arthritis's molecular bases and other immune mediated disease.

Methods: We conducted a systematic review focusing on immune molecules presents in different autoimmune conditions of our choice. The bibliographic research was done through Medline (PubMed), Google scholar and AEPED.

Results: A total of 15 papers from different countries were evaluated and reviewed, dealing with JIA's and other immune diseases molecular bases.

Conclusions: most autoimmune diseases discussed responded to the same group of medicaments. Further investigation is needed as information is scarce. No evidence has been yet found regarding their underdiagnosis and its correlation with their molecular bases.

Content index

Key words

ANA: anti-nuclear antibodies

ATB: antibiotics

CNO: non-bacterial osteomyelitis

COX: cyclooxygenase

DM1: Type 1 Diabetes mellitus

DMARDs: Disease-modifying antirheumatic drugs

ELISA: enzyme linked immunosorbent assay

ERA: Enthesitis-related arthritis

HA20: A20 haploinsufficiency

HbAc1: Glycated haemoglobin

HLA: Human leukocyte antigen

IFN: interferon

IL: Interleukin

ILAR: International League of Associations for Rheumatology

JIA: Juvenile idiopathic arthritis

JPA: juvenile psoriasic arthritis

LPS: lipopolysaccharides

MAS: Macrophage activation syndrome

MHC: major histocompatibility complex

MRI: Magnetic resonance imaging

MTX: methotrexate

NK: natural killer

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RA: reactive arthritis

RF: rheumatoid factor

RS: Reiter's syndrome

SLE: systemic lupus erythematosus

TNF: tumour necrosis factor

UPSA: undifferentiated peripheral spondylarthritis

Table index

Figure Index

1. Introduction

1.1. Juvenile idiopathic arthritis (JIA)

1.1.1 Definition

JIA is a variety of immune mediated diseases of unknown origin that affects children below the age of sixteen for a minimum of six ongoing weeks. It usually presents itself attached to joint inflammation, rigidity, and loss of movement.

Aversely to adult rheumatoid arthritis, JIA it is usually outgrown by those suffering from this condition. However, poor bone development remains a possibility in those in growth when affected by this condition (1,2).

1.1.2 Classification

The ILAR (International League of Associations for Rheumatology) classifies the JIA in in seven categories which typically manifest with distinctive symptoms. These divides children helping to orientate treatment (3).

Systemic juvenile arthritis: it represents between a 10-20% of those affected by JIA, in this subtype children do not only have their joints strained but also other organs such as their liver or lungs. Moreover, a patterned fever once or twice a day must be present for over two weeks. This type commonly is of a more complex determination since it typically consists of an exclusion diagnosis (3,4).

Oligoarticular Juvenile Idiopathic Arthritis: this subtype is characterized by affliction of four or fewer joints. Affection is typically present in weight-bearing articulations, specifically knees and ankles that can lead to limb trauma, muscle atrophy and length discrepancy in lower extremities (3).

Polyarticular Juvenile Idiopathic Arthritis: which can also be divided in seropositive and seronegative rheumatoid factor polyarticular arthritis. That consist in individuals with simultaneous affection of five or a greater number of hinges in the first 6 months within onset. To sum up, small joints are commonly injured as well as bigger (3).

Psoriatic arthritis: manifestations usually begin with arthritis preceding psoriasis signs. Most commonly affecting females in a biphasic distribution that peaks at 2-4 and 9-11 years old.

Enthesitis-related arthritis (ERA): children display a combination of joint, tendons, and ligaments inflammation, making the distinction between arthritis and spondyloarthropathy nearly inexistent. Many authors establish enthesitis-JIA to be an association of both conditions. Tendon and ligament soreness can also be found in oligoarticular and polyarticular subtypes yet the development of hinge inflammation in a previous enthesitis seems more plausible with spondyloarthropathy (3).

Undifferentiated arthritis: its diagnosis requires either for the individual to not present any conditions or fulfil criteria for more than one category.

ILAR Characteristics of presentations, frequency, onset age, gender distribution and diagnostic criteria are showcased in the figures below.

Table 1. JIA subtypes and their diagnosis criteria (5)

Disease (Onset type)	Disease (Course subtype)	Criteria	Exclusions
Systemic Arthritis		*Definite:* 1. Quotidian fever for at least 2 weeks 2. Evanescent, non-fixed erythematous rash 3. Arthritis *Probable:* In the absence of arthritis, 1 and 2 (above) plus any two of: 1. General lymph node enlargement 2. Hepatomegaly or splenomegaly 3. Serositis	NOMID[a] Periodic syndromes[b] Drug hypersensitivity
Polyarthritis RF-		Arthritis of ≥5 joints during the first 6 months of disease	Positive RF[c]
Polyarthritis RF+		1. Arthritis of ≥5 joints during the first 6 months of disease 2. Positive RF on at least two occasion 3 months apart	Psoriasis
Oligoarthritis	Persistent Oligoarthritis	Arthritis of 1-4 joints during the onset or course of the disease	Psoriasis Positive RF
	Extended Oligoarthritis	1. Arthritis of 1-4 joints during the first 6 months of disease 2. Arthritis of ≥5 joints after the first 6 months of disease	Psoriasis Positive RF
Enthesitis - related arthritis		Arthritis and enthesitis or, Arthritis or enthesitis with at least two of: 1. Sacroiliac joint tenderness and/or inflammatory spinal pain 2. Presence of HLA B27 3. Family history in at least one first- or second-degree relative of medically confirmed HLA B-27-associated disease 4. Anterior uveitis that is usually associated with pain, redness or photophobia 5. Onset of arthritis in a boy after 8 years of age	Psoriasis confirmed by a dermatologist in at least one first- or second-degree relative Presence of systemic arthritis
Psoriatic arthritis		Arthritis and psoriasis or, Arthritis and at least two of: 1. Dactylitis 2. Nail pitting or onycholysis 3. Family history of psoriasis in a first-degree relative	Positive RF
Other		Arthritis for ≥6 months and does not fit into any of the above categories or fits into more than 1 category	

[a] Neonatal onset multi-system inflammatory disease

[b] Including familial Mediterranean fever, hyper-IgD syndrome, FAPA (fever, aphthous ulceration, pharyngitis, adenopathy)

[c] RF=Rheumatoid factor

Table 2: frequency, age of onset and gender distribution of JIA subtypes (6, Monah, T. 2019)

TABLE

Key characteristics of JIA subtypes: Frequency, age of onset, gender distribution[11]

Subtype	% of all cases of JIA[a]	Age of onset	Gender distribution
Enthesitis-related arthritis	3-11	Late childhood and adolescence	Highly predominant in females
Extended oligo-articular arthritis	27-56	Early childhood (peaks at 2-4 y)	Exceedingly predominant in females
Psoriatic arthritis	2-11	Biphasic distribution (early peak at 2-4 y, later peak at 9-11 y)	Predominant in females
Rheumatoid factor-positive polyarthritis	2-7	Late childhood and adolescence	Highly predominant in females
Rheumatoid-factor-negative polyarthritis	11-28	Biphasic distribution (early peak at 2-4 y, later peak at 6-12 y)	Highly predominant in females
Systemic arthritis	4-17	Throughout childhood	Equal
Undifferentiated	11-21	—	—

JIA, juvenile idiopathic arthritis.

[a] As variously reported in the literature.

Source: Adapted from Basra HAS, et al. *Br J Radiol*. 2017.[11]

1.1.3 Epidemiology

The most common chronic rheumatologic disorder during childhood is nowadays JIA. Females are commonly affected with a **2.9 a 35,4/100.000** ratio in girls and **1.7 a 19.3/100.00** ratio in boys. In the systemic JIA, dissimilarities cannot be found among both sexes and in enthesitis-JIA males are the majority hit by the condition. Incidence and prevalence may vary being most definitely due to an underdiagnosis, however, it is estimated that globally it is range of occurrence oscillates between **1,6-23 / 100.000** children under sixteen affected/ year. And its prevalence approximates to **3,8-400/ 100.000** (7).

Oligoarticular JIA is the most quotidian in our field followed by the polyarticular form, being the rarest diagnosis, it is psoriatic kind.

1.1.4. Aetiopathogenesis

There are two main systems JIA can be mediated, systemic JIA is the only autoinflammatory variety whilst the remaining are immunologically dependent.

JIA is believed to be a multifactorial disease; many mechanisms are described that include genetics and immune processes. Systemic JIA is an exception, as it holds autoinflammatory bases along with native immunity alteration.

In the present days, it is known that systemic JIA is a manifestation of native immunity dysregulations characterized specifically by aberrant phagocytes activation, leading to an increasing amount of autoinflammatory cytokines being the most relevant the following interleukins (ILs): IL-6, IL-18 and S100 proteins, responsible for its distinct autoinflammatory disease clinical manifestations.

On the other hand, oligoarticular and polyarticular forms manifestations are due to autoimmune responses mediated by TCD4+ lymphocytes activated by autoantigens, driving to a dysregulation, increasing titles of Th17 and Th1 cells and descending regulatory T cells, causing and error in tolerance against autoantigens and an expansion in proinflammatory cytokines such as IFN-ϒ and IL-17 holding back anti-inflammatory cytokines. These types of JIA have a certain association with human leukocytary antigens: HLA-A2/oligoarticular JIA, HLA-DRB1/seronegative polyarticular JIA, HLA-DR4/seropositive polyarticular JIA.

Psoriatic and enthesitis related JIA are recognized to have some association with lymphocyte TCD8+ response and augmentation of cellular expression of tumour necrosis factor (TNF) α and HLA-B27 is linked to spondyloarthropathy and seems to have a strong association with enthesitis JIA usually determining various cases amongst the family.

1.1.5.1. Risk factors

Multiple papers have now been published trying to correlate environment factors as triggers in distinct categories of JIA such as vaccines, breastfeeding, or trauma. Thus, poor correlation has been found between atmosphere and JIA besides genetic predisposition (7).

What has been found to make children more prone to JIA development is the female sex and children aged 2-3 years old are at their peak of developing this disease (8).

Furthermore, underlying risk factors for numerous diseases such as maternal prenatal smoking, breastfeeding, hospitalization during first year of life or day care for the first six years have not been found to be linked to JIA development (9).

1.1.6. Clinical manifestation

Articulation inflammation, pain and stiffness are the most frequently manifestations related to JIA. JIA's onset tends to follow an insidious trajectory and has a tendency to present occasional limb and morning rigidity that show signs of improvement during the day. Lactating children are usually unsettled and refuse to wander. In advanced stages joints are witnessed to be enlarged, warm to the touch and its movement appears to be reduced with occasional pain to mobilization.

Oligoarticular JIA consists of predominant affectation of weight-bearing joints, especially knees and ankles. Being the category with the biggest rate of uveitis risk.

Polyarticular serotypes tend to be symmetrical, emerging in both lower and upper limbs and even affecting small articulations in hands and feet. Rheumatoid Factor (RF) Seropositive type will follow a similar path to that proper of the adults, developing micrognathia secondarily to temporo-mandibular joint. It is also conceivable to find cervical intervertebral affectation continued by a reduced extension of the neck (7).

Enthesitis related JIA is usually asymmetrical and peripherical, affecting main joints such as knew, ankles and hips. Axial signs are uncommon during childhood, being more prone to be developed in adults.

Psoriatic JIA is asymmetrical too and can be found in big and small hinges being characteristic the presence of dactylitis and ungual pitting (7).

Complications are not an exception in JIA, being uveitis the most frequent extraarticular manifestation. It usually presents itself as an anterior chronic uveitis within the first four years of the pilot stages of JIA. It is mostly bilateral, recurrent, and asymptomatic and several

will need close tracking. First ophthalmologist appointment should coincide with the commencement and should be continued if there is vision compromise to prevent irreversible sight loss.

Macrophage activation syndrome (MAS) is another possibly mortal complication specific for systemic JIA. Appearing in up to 10% of the patients. MAS is an uncontrolled lymphocyte T proliferation and massive cytokines macrophage synthetization resulting in cytochemical storm (7).

1.1.7. Diagnosis

Confirmation of JIA is complex, there are no specific laboratory nor image tests to diagnose patients suffering from this disease. Therefore, JIA diagnosis algorithm is based in exclusion of other illnesses that can be manifested in similar ways, based in anamnesis and physical examination.

During anamnesis questions oriented towards identifying inflammatory pain, which is morning predominant, with rigidity that improves along the day, may be crucial for outlining a possible JIA.

Physical examination is also important, having to pay special attention to salmon, evanescent rashes, hepatosplenomegaly and adenopathies. Inspecting every joint for tumefaction, temperature and pain as well as evaluating muscular strength is equally relevant (7).

Laboratory tests should be conducted before any suspicion. Hemogram, biochemistry and acute phase reactants are significant. Other test such as uric acid, muscular enzymes and serologies can be helpful to discern over other possible etiologies. Even though there is no precise test for stablishing a diagnosis, anti-nuclear antibodies (ANA), Human leukocyte antigen (HLA) B27 and RF determination can be useful to classify patients in different subtypes. However, these markers can be also present in healthy children, making them not specific.

Radiology tests are also not precise but can be convenient to differentiate other conditions such as tumours or trauma.

1.1.8. Treatment

Target of treatment is not to cure, but to help children suffering from JIA maintain a decent quality of life, socially and physically activity. Doctors use a combination of strategies to alleviate inflammation and pain, maintaining joint movement and strength. Treatment must be initiated prematurely to attempt acquire a better response. Drugs used must be determined individually depending on age, kind, onset, and gravity of JIA (10).

JIA's treatment consists in a therapeutic ladder.

First step is to prescribe nonsteroidal anti-inflammatory drugs, these, are only used as a symptomatic treatment, inhibiting the cyclooxygenase (COX), and interfering in prostaglandins synthesis. These are not disease modifying and are generally used during preliminary stages while we try confirming JIA diagnosis (11).

The second step will be adding corticosteroids to our treatment plan, these are not only anti-inflammatory as the ones previously mentioned, but also carry immunosuppressive capability. Corticosteroids are typically used as a waiting treatment while we wait for effectiveness of other drugs. However, they can be the chosen therapy for severe cases with systemic effects (11,12).

Short use is normally desired as corticosteroids possess side effects and should be combined with calcium and vitamin D.

Disease-modifying antirheumatic drugs prescription is the third step during JIA's treatment. The drug of choice is Methotrexate as a remission inducer, establishing the main therapy axis in JIA affected patients. Most everyday use drugs are shown in the table below.

Table 3. Their step in JIA's treatment. Self-made base on (11,12. Elordy 2020)

DRUG	**DOSE**	**MECHANISM**
Methotrexate (MTX)	10-15 mg/m^2 a day	Dihydrofolate reductase inhibition
Sulfasalazine	<30 kg 50mg/kg a day	Inhibits prostaglandins

Table 3. Their step in JIA's treatment. Self-made base on (11,12. Elordy 2020)

Leflunomide	<20-40 kg 100mg load then10mg >40kg 100mg load then 20mg	Inhibits pyrimidine synthesis
Hydroxychloroquine	4-6 mg/kg a day	Lysosomal membrane stabilization and IL-1 reduction and TNF synthesis

The fourth and last step in the therapeutical ladder are biological agents. These have specific actions against inflammatory response cells and are for hospital use only, either intramuscular or intravenous (13). Those most used are displayed in the table below.

Table 4. Last step on JIA's therapeutic ladder (13)

Name	**Infliximab** (REMICADE®, vial 100mg)	**Etanercept** (EMBREL®, jeringa 25 mg and 50mg)	**Adalimumab** (HUMIRA®, jeringa/pluma 40mg)	**Abatacept** (ORENCIA®, vial 250mg)	**Tocilizumab** (ROACTEMRA®, vial 20mg)	**Rituximab** (MABTHERA®, vial 100mg and 500mg)
Characteristics	Chimeric monoclonal antibody anti-TNF	Fusion protein that adheres to the TNF receptor (p75)	Monoclonal humanised antibody Recombinant anti-TNF	Fusion protein (formed by an modified fragment of human IgG1 and a extracellular domain of antigen 4 associated with del ant geno 4 citotoxic T linfocyte)	Monoclonal humanised antibody Recombinant anti- IL-6	Chimeric monoclonal antibody anti-CD20
Dose	3mg/kg i.v. weeks 0, 2, 6. then, every 8 weeks	25mg s.c./2 times week or 50mg s.c./week	40mg s.c. every 2 weeks	10mg/kg i.v.: <60kg: 500mg 60-100kg: 750mg > 100kg: 1000mg week 0, 2 and 4, then every 4 weeks	8mg/kg i.v. (minimum dose 480mg every 4 weeks)	1000mg i.v. days 1 y 15

Prior to initiating biological agents' treatment, patients must be evaluated for tuberculosis, HIV, B and C hepatitis virus, aside from periodical blood work to discard cytopenia of recent

appearance. as well as keeping their vaccination calendar up to date to help prevent emergent infections.

When complications are stablished, they ought to be treated specifically. Uveitis treatment is based on corticosteroids and topic cycloplegics. However, a second line treatment such as MTX can be added if previous treatment does not show signs of improvement, even making it necessary in some cases to add biological agents. Macrophage activation syndrome needs prompt treatment, including intravenous bolus of corticosteroids. Support measures are also needed as in every life-threatening disease[7,10].

Some doctors recommend parents to take their children to physical or occupational therapy, to help with joint flexibility preservation and muscle tone. and even may suggest the use of splints or hinge support devices to keep articulations in a functional position. In extreme cases surgery can be proposed for correcting and improving function[10].

1.1.9 Prognosis

Prognosis has shown improvement (7).

Numerous scales have been found to be useful in evaluation and tracking of patients. Oligoarticular JIA has shown the best prognosis with remission in nearly 50% of patients in 5-10 years within onset. Polyarticular JIA forms are usually more aggressive not entering remission spontaneously. Enthesitis related JIA evolves to ankylosing spondylitis in even 25% of patients. Psoriatic JIA will enter remission stages in over 35% of cases (7).

1.1.10 JIA currently

JIA is currently the most common chronic rheumatic disease in children (1,2). Nowadays it is known that is not a solely identity, but it consists of a variety of different diagnosis (1). Current underdiagnosis is a barrier that puts stop to treatment and investigation of this disease. Being a children's disease is relevant when thinking about treatment as infants possess characteristics we need to consider (7). We now know that JIA is not of such positive prognosis as we thought. In many cases patients do not enter remission and the disease continues to havoc for years, deteriorating children's quality of life. Treatment requires a

multidisciplinary collaborative towards stabilisation and amelioration of clinical manifestations (14).

1.2. Immune bases

1.2.1. ANA

ANAs are autologous cell and cytoplasmatic component directed immunoglobulins. ANA are usually found in and related with rheumatic diseases and its determination must be done with immunofluorescence, with Enzyme Linked Immunosorbent Assay (ELISA) or western blot confirmation. Despite its high sensitivity, ANA are not specific of any rheumatic illness and are present in close to 100% of rheumatic patients and in 3-15% healthy population. It is not a valuable parameter due to non-specificity (15). Making

solely helpful for stablishing existence of an autoimmune disease (15)

1.2.2. Major histocompatibility complex (MHC)

The HLA system is a crucial part of the immune system, being controlled by genes coded in chromosome six, it encodes surface molecules in charge of antigenic peptide presentation to T-cell receptors. There are two main classes, class I and II. There are two main types of HLA.

MHC I: transmembrane glycoproteins molecules are present on the surface of nucleated cells. The consist of an alpha heavy chain bound to a beta2 microglobulin with two binding domains. The heavy chain is encoded for genes HLA-A, HLA-B AND HLA-C. TCD8+ cells are the ones reacting with this kind of major histocompatibility complex. Often having cytotoxic function, these cells require to be capable of recognizing infected cells (16).

MHC II are present on antigen-presenting cells, activated T cells or interferon gamma induced cells. Its molecules consist of two polypeptide chains alpha and beta, having each two domains, a peptide-binding domain, and an Ig-like domain. HLA-DP encodes these chains, -DQ, or -DR genes. T cells that react to MHC II molecules express CD4 and are usually helper cells[15]. HLA-B27 allele, present in type I MHC is associated with many

autoimmune conditions, in JIA it can be present in patients affected with enthesitis JIA kind and most definitely related with ankylosing spondylitis, making it plausible for patients with this form of JIA to develop a spondylitis over the years. Nevertheless, HLA-B27 is also present in 5-15% of general population making it a nonspecific determination for diagnosis (16).

1.2.3.TNF-α

Tumour necrosis factor is an inflammatory macrophage and monocyte produced cytokine in the course acute inflammation, responsible of signalling events it leads to necrosis or apoptosis which makes it important in infection and cancer resistance. TNF-α conducts its effects primarily by binding 55 kDa or 75 kDa cell membrane receptor. The defining attribute of TNF is an extracellular domain consisting in 2-6 cysteine rich repetitions. Supplementarily, structurally related "decoy receptors" take over TNF molecules rescuing cells from apoptosis (17).

TNF-α mediates in psoriatic and enthesitis forms of JIA, in which abnormal presence of inflammatory cytokines are synthesised in joint synovial membrane. TNF-α has a crucial role in initiating, perpetuating, and destroying synovial tissue expressing proinflammatory genes such as IL-6, IL-1, and IL-18. These cytokines activate fibroblasts, which synthesise matrix metalloproteases that demolish cartilage, and osteoclasts leading to complete articulation architecture destruction.

This same cytokine has been found to be linked in Systemic Lupus Erythematosus (SLE), although its roll remains controversial, higher title of TNF-α have shown relation with autoantibodies and kidney damage.

In Type 1 Diabetes mellitus (DM1), TNF-α plays a cytotoxic roll in pancreatic islets inducing apoptosis of β cells and inhibits insulin secretion. It has also been linked to inflammation of β cells, showing dendritic cells and macrophages present in initial stages of the diabetes (17).

1.2.4. S100 proteins

S100 proteins are a family of twenty-four calcium binding cytosolic proteins distributed in intracellular, extracellular and both regulatory effects. S100 proteins participate in regulation of proliferation, differentiation Ca^{2+} homeostasis, inflammation amongst an array of other functions participating in adaptive immunity, tissue development and repair (18). S100 proteins take part in inflammation mediated responses being released with cell stress or inflammation to an acellular compartment binding to surface receptor and activating intracellular signalling pathways such as cell migration, proliferation, apoptosis or swelling (19). Systemic JIA and LSE are associated with S100 protein activation making its determination useful for distinguishing other fever and autoinflammatory syndromes.

1.2.5. Interleukins

ILs are cytokines expressed not only by leukocytes, which was first thought, but in many other cells. Their role is vital in immune cells differentiation and activation, as well as pro-inflammatory and anti-inflammatory properties. Primary functions of interleukins include activation during an inflammatory or immune process having both paracrine and autocrine functions. Interleukins frequently influence other interleukin synthesis and actions (20,21).

Table 5. source, target cells and function of the most relevant interleukins. Self-made based on (20. Valliant, J. 2022)

INTERLEUKINS	Source	Target cells	Effect
IL-1	- Macrophages - Lymphocytes - Fibroblasts - Astrocytes	- T cells - B cells - Macrophage - Endothelium cells	- Lymphocyte activation - Macrophage stimulation - Leucocyte adhesion - Cell apoptosis - COX-2 initiation

Table 5. source, target cells and function of the most relevant interleukins. Self-made based on (20. V Valliant, J. 2022)

			- Type 2 phospholipase A activation. - Fever
IL-6	- Macrophages - T cells - B cells - Fibroblasts	- Hepatocytes - B cells - T cells -Fibroblasts	- B cell differentiation - Acute phase reactants synthesis
IL-18	- Macrophages - Lymphocytes - Dendritic cells - Non-immune cells	- Th1 cells - Natural Killer (NK) T cells	- TNF-α production. - Enhances NK cell activity. - Increases molecule adhesion. - Promotes infiltration of inflammatory immunocompetent cells into extravascular space.
IL-17	- Th17 - ϒO T cell - LTi - ILC3 - NK - Neutrophils - Macrophages	- Epithelial cells - Endothelial cells - Fibroblasts - Osteoblasts.	- TNF production - Promotes neutrophilic inflammation - mediate protective innate immunity.

1.3. Immunologically mediated diseases

1.3.1. Ankylosing spondylitis

Ankylosing spondylitis is a rheumatic disease that cause particularly spine bones to fuse, reducing spine flexibility and resulting in hunched posture, and even breathing difficulties. It affects more men than women and early signs tend to appear in early adulthood.

As most rheumatic diseases ankylosing spondylitis has no specific cause despite HLA-B27 gene having been shown to be involved in higher risk of developing the disease; not every HLA-B27 presenting person will develop the disease, nonetheless. Progression prevention and quality of life improvement is treatment's main target (22).

1.3.2. Systemic Lupus Erythematosus

SLE is an autoimmune disease that assaults healthy tissue in the body affecting multiple organs. Aethipathogenesis is unknown, but it may be linked to a range of factors such as genetics, environment, and drugs. SLE is more common in women with a proportion of 10:1 being young women between the age of 15-45 the most affected patients (23). Symptoms are diverse including joint pain, fever without a focus, sensitivity to sunlight, blood vessel inflammation, blood clots, and a "butterfly" like malar rash after sunlight exposure being developed in 50% of SLE patients. To be diagnosed with SLE patients must present at least four of the eleven primary signs of disease. As most autoimmune diseases SLE has nowadays no permanent crisis eradication, following an escalating therapeutic ladder consisting in nonsteroidal anti-inflammatory drugs, corticosteroids, methotrexate, and immunosuppressive medicines; but most importantly doctors should always recommend hygienic-dietary measures (23).

Table 6. SLE symptoms and their frequency. Self-made. Adapted from reference 24 (Mageed. S.A. 2019).

Clinical feature	**SLE**
Photosensitivity and malar rash	Common
Proteinuria	Common
Neuropsychiatric symptoms	Common
Oral ulcers	Common

Table 6. SLE symptoms and their frequency. Self-made. Adapted from reference 24 (Mageed. S.A. 2019).

Arthralgia	Common
Haemolytic anaemia	Common
Kayser-Fleischer ring	Not common

1.3.3 Uveitis

Autoimmune uveitis is an autoinflammatory process of the uveal components due to an aberrant reaction to the patient's own cells which can cause irreversible damage to other parts of the eye such as the retina, vitreous body and optic nerve and is usually presented associated with other immune mediated diseases, for instance reactive arthritis (RA) or SLE, being in many cases the initial presentation. Clear association with HLA-B27 has been established a higher risk of autoimmune uveitis and may be considered a different clinical disorder and is associated with systemic diseases such as, Reiter's syndrome (RS), JIA, and psoriatic arthritis (25).

The internal uveitis study group standardizes classification in anterior uveitis and intermediate uveitis depending on its primary inflammation site.

Typical symptoms are blurred vision, photophobia, eye pain, floaters, and injected conjunctiva, however children may present themselves as asymptomatic. The occurrence of these symptoms should orientate to a uveitis and an ophthalmological examination in slit-lamp, visual acuity, eye fundus and intraocular pressure must be completed, as well as microbiology to see anterior chamber cells, lately completing its medical history to rule out other disorders. On the other hand, parts of the body need to be examined to discard presence of other immunologically mediated diseases (25).

1.3.4 Type 1 Diabetes mellitus

DM1 is a chronic disease in which level of sugar in the blood is high due to lack of insulin which is normally produced in by beta cells and is needed to move glucose into cells so it can be stored and later used for obtaining energy. In DM1, β cells produce little to no insulin making it impossible to keep up with body requirements and glucose building up in the bloodstream resulting in a constant hyperglycaemia (26).

The exact etiology is unknown; however, we now know that it occurs when the immune system mistakenly destroys healthy tissue. This disease is often diagnosed in preliminary stages of life after a many times severe decompensation. Symptoms include thirst, hunger, polyuria, blurry vision, and asthenia. Treatment consists in subcutaneous or pumped insulin combining rapid acting insulin with delayed release insulin. To have a healthy lifestyle and follow the prescribed treatment should achieve an excellent control of glucose levels and prevent serious complications that type 1 diabetes patients will always have to attempt to avoid (26).

1.3.5. Reiter Syndrome

RS is studied within reactive arthritis and is characterised by eye, joint, urethra and skin affection. This syndrome can present a countless number of symptoms in various organs, however, not every symptom may occur simultaneously, coming in quickly or insidiously accompanied of recurrences and remissions. It is recognized to be present specially in male patients between the ages of 20 and 40, making HIV coincident infection a high-risk factor. Being sexually transmitted infections typically present before Reiter's syndrome onset. Reactive arthritis etiology is still obscure, then again research insinuate genetic predisposition related to HLA-B27 allele (27).

Symptoms include painful urination and discharge along with a urethritis usually followed by a 4–28-day duration arthritis affecting small joints of hands and feet, ankles, hips, and knee articulations. Eye inflammation, mouth ulcers, keratoderma blennorrhagica and back pain could be present as well.

Reaching a diagnosis can be intricate as symptoms may occur weeks apart, normally diagnosing Reiter's syndrome when eye and urethra affections coincide with arthritis manifestations as there are no specific tests for reactive arthritis. Blood work typically shows positive HLA-B27, elevated white blood cell count and increased Erythrocyte sedimentation rate. Imaging tests can show bone loss areas, osteoporosis signs or bony spurs if joints have been repeatedly inflamed. RA treatment consists in responsible infection microorganisms' eradication with antibiotics, and arthritis treatment such as anti-inflammatory medication and MTX (27).

1.3.6. Hashimoto's thyroiditis

Hashimoto's disease is an autoimmune disorder often cause of hypothyroidism and rarely overactive thyroid gland. The immune system produces antibodies that attack the thyroid gland, making white blood cells to build up in the thyroid becoming damaged and lacking capability of thyroid hormones production (28).

Hashimoto's is between 4 to 10 times more common in women than it is in men. Despite being plausible to find teen women affected it more often develops in older women aged 30-50. Other autoimmune disorders and Hashimoto's disease affected family members increase the risk of Hashimoto's development, however, its origin is still unknown.

Symptoms of hypothyroidism are fatigue, weight gain, cold feeling, joint and muscle pain, constipation, dry skin and hair, fertility problems and bradycardia. Untreated thyroiditis may

lead to complications that include high cholesterol, heart failure, high blood pressure and problems during pregnancy (28).

Diagnosis must include a thyroid examination typically finding a swollen neck and enlarged gland (goitre) that may produce throat fullness sensation without pain. Blood test will be run to diagnose hypothyroidism and its origin.

Treatment is usually simple and depends on whether the thyroid gland is capable of to produce enough thyroid hormones or not. Levothyroxine, which is identical to T4 natural hormone, is used to treat hypothyroidism of all origins. Dietary-hygienic recommendations may also be given to patients, recommending taking the drug on an empty stomach and before 30-60 minutes prior to their first meal (28).

Children are rarely affected by immune diseases, nevertheless, when they are, prompt treatment can result in quality of life, and prognosis improvement additionally it can prevent irreversible damage in adulthood. And so, a prematurely made diagnosis can benefit patients suffering from JIA. JIA goes unnoticed in most cases, leading to underdiagnosis which can carry negative effects on children affected by this condition when they grow older. Therefore, the study of JIA becomes important.

2. Hypothesis

The PICO process is a helpful method used in evidence-based procedures to formulate answers in medical and health care fields. Moreover, it can be used to improve search strategies such as systematic reviews.

- P → population: Children under 16 affected by JIA
- I → intervention: molecular bases and biomarkers such as
- C → comparison: immunologically related diseases
- O → outcome: underdiagnosis improvement

¿Is there a relationship between JIA's molecular bases, other immune mediated diseases and their underdiagnosis?

3. Objectives

The main goal is to deepen into autoimmune pathologies' molecular bases, primarily JIA.

Emphasizing on its underdiagnosis is key, so additional studies can be conducted as children affected typically have a mediocre quality of life.

Specific objectives:

- Conducting a systematic review on JIA biomarkers evaluation.
- To deepen into possibly affected molecular bases in JIA.
- Diagnosis process evaluation in JIA and immune related diseases.

4. Material and methods

4.1. Methodological approach

The review will be done following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) method. PRISMA is and evidence-based items method used in systematic reviews. The initiative behind is to address enduring issues and lack of transparent review methods in already published papers and to internationally unify systematic reviews. Its last rework has been approved in 2020 which will be the diagram followed in this bibliographic review.

This systematic review was carried through a cross-sectional descriptive bibliographic study. Being the papers retrieved via bibliographic review.

All data used has been acquired through direct internet consultation. Being specific medicine data bases used Medline (PubMed), Google scholar and AEPED (Spanish association of paediatrics' primary care).

4.2. Research strategy

Research strategies have been developed combining the use of free text in the abstract and title fields as well as controlled vocabulary present in medical thesaurus (MESH)

Terms used include: "AIJ", "juvenile arthritis", "idiopathic juvenile arthritis", "children", "juvenile chronic arthritis", " juvenile rheumatoid arthritis", "still disease", "underdiagnosis", "leukocyte antigens", "histocompatibility", "HLA antigens", "human leukocyte antigens", "cell growth factor", "IL-6 receptor", "IL-6", "IL-18", "IL-18 receptor", "TCGF receptor", "helper cells", "helper inducer T lymphocytes", "helper T-cells", "helper inducer T-cells", "calcium binding protein", "vitamin D dependent calcium binding protein", "lymphotoxin", "lymphotoxin alpha", "tumour necrosis factor beta", "soluble lymphotoxin-alpha", "ANA", "antinuclear antibodies", "anti-DNA antibodies", "antinuclear antibody", "Libman sacks disease", "uveitis", "diabetes", "ankylosing

spondylarthritis", "chronic lymphocytic thyroiditis", "Hashimoto thyroiditis", "Hashimoto syndrome". Terms were combined with the help of Boolean operators (AND) and (OR).

In addition, manual research has been performed on the bibliographic references of the included studies, to try an include papers that might have gotten unnoticed and reach a higher number of articles on the topic, as not much investigation has been done in this matter.

The research and posterior selection have been done between December 2022 and April 2023

4.3. Inclusion and exclusion criteria

4.3.1 Inclusion criteria

Articles dealing with JIA or immune diseases of interest.

Articles published in English or Spanish.

All type of studies.

4.3.2 Exclusion criteria

Studies that include patients older than 16-year-old.

Articles not contributing to achieve the objectives of this study or do not complement it.

Opinion pieces.

4.4. Document selection

This review's author personally appraised articles. Paying special attention to titles, abstracts, and keywords to determine the relevance and satisfactory fulfilment of inclusion criteria in concurrence with the main supervision professor.

Those articles that were helpful but not free, where obtained through the "Basic immunology investigation unit" from Universidad Católica de Valencia supplied by Dr Ignacio Ventura.

4.5. Review's Limitations

The possibility of some article being missed through the paper selection remains due to a scarce number of people involved. Being exclusively the author and the collaborator, the ones conducting the article triage.

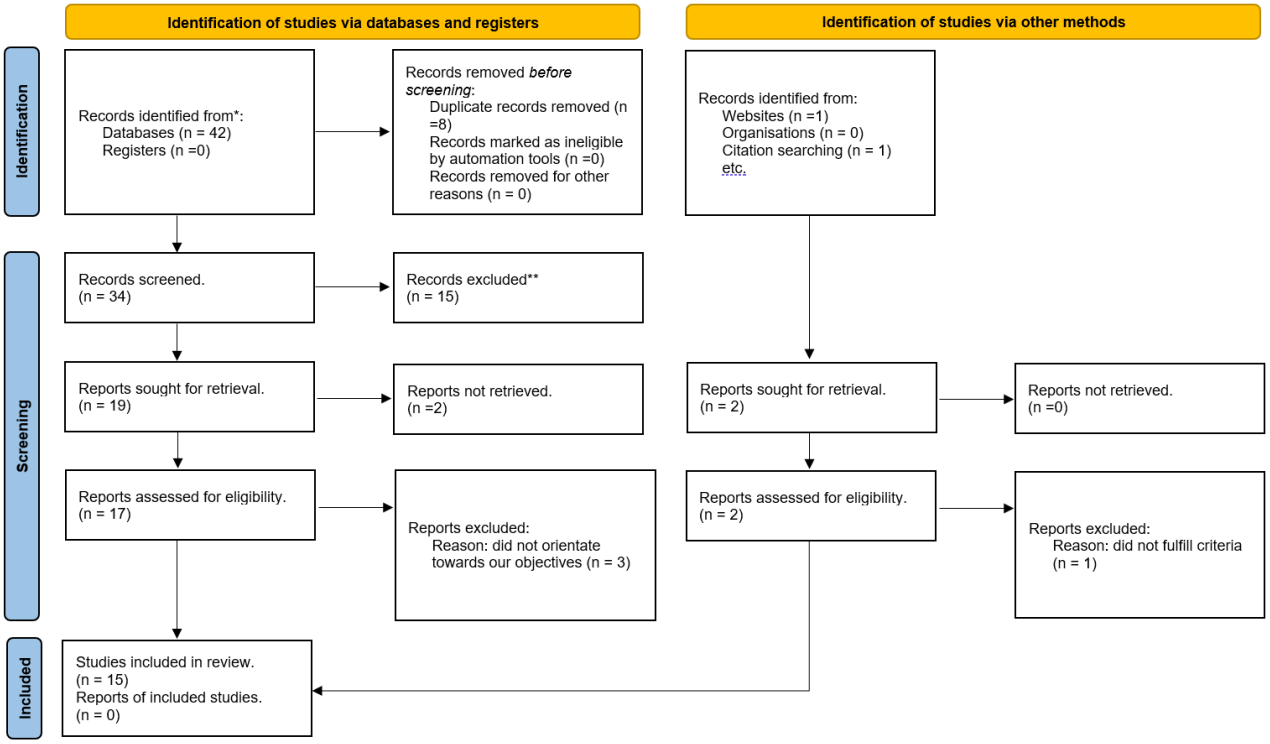
In addition, relevant studies might go undetected in relation with our assembled research strategy. Even so, large efforts have been put to prevent great article loses, maximizing the sensitivity of our strategy by including synonyms or alternative terms of the same concept and manually revision of bibliographic references which are believed to have helped minimize the unseen papers number.

Lastly, some reports may not comply with part of the information required as number of articles fit for this study is considerably low.

5. Results

5.1.- Articles included in the review

Figure 1. PRISMA flowchart. Source: Self-made



As shown in the flowchart above, we have included 15 articles in this review. All of them have been individually analysed. Moreover, all of them have been read, summarized, and disposed in the table below.

Table 7. Table of results. Self-made

Study	Population	Sample size	Date & country	Study type
Olivieri, AN. et al. (29)	Teenage girl affected with JIA, Hashimoto's and DM1	N= 1	Italy 2013	Case report

Harms, RZ. et al. (30)	DM1 juvenile patients and healthy controls	N=63	USA 2020	Case-control
Koskit, MM. et al. (31)	Children affected either by CNO, JIA or DM1 And healthy controls	N=117	Russia 2021	Prospective case-control study
Angeles-Han, ST. et al. (32)	Children affected with JIA related uveitis and healthy controls	N=40	USA 2017- 2020	Case-control study
Van Strealen, SW. et al. (33)	Patients that met the ILAR criteria for JIA	N= 5529	Multiple countries 2011-2019	Cohort study
Shin, Y. et al. (34)	Children diagnosed with uveitis	N=155	South Korea 2005-2018	Observational study
Morelle, G. et al. (35)	Children diagnosed with non-infectious chronic uveitis.	N=147	France 2010-2017	Descriptive, observational, retrospective and bicentric study
Wang, J. et al. (36)	Patients diagnosed with JIA related uveitis and healthy controls.	N= 30	China 2021	Observational study

Tappeiner, C. et al. (37)	Children with less than 1 year of JIA diagnosis	N= 954	Germany 2014-2018	prospective, controlled, observational, multicentre study
Zhang, D. et al. (38)	Children diagnosed with A20 haploinsuffiency	N= 3	China 2016-2019	Case report
Leerkvaleekul, B. et al. (39)	SLE affected children with active disease	N=102	Thailand 2015-2018	Cohort study
Räisänen, L. et al. (40)	Children born between 2000-2005 in Finland	N=11.407	Finland 2000-2018	Register-based cohort study
Parida, JR. et al. (41)	Children affected with Reiter syndrome or undifferentiated spondylarthritis	N= 100 cohort I N= 38 cohort II	India 2020	Comparative cohort study
Geneva, M. et al. (42)	JIA patients younger than 16 years old and less than a 12-month diagnosis	N=266	Germany 2020-2021	prospective observational, multicentre study
Rumsey, DG. et al. (43)	Children with enthesitis related arthritis or juvenile psoriasic arthritis	N=902	Multiple countries 2018-2021	Case report based on Observational study

All the papers included count with references to JIA and other immune diseases such as: Hashimoto's disease, SLE, spondylitis, uveitis, and diabetes. In addition, all of them include either immune molecules and/or markers references or treatment allusion.

Of the 15 articles included, 5 where observational studies, 4 were cohort studies, 3 consisted of case reports and 3 were case-control studies.

Due to lack of investigation, most studies were conducted in different countries, the top countries were the USA with 2, Germany and China with 2 studies each, Russia, Italy, Thailand, South Korea, France, Finland, and India all contributed with 1 study each and surprisingly, there were 2 studies that included different countries contributions.

Refractory RF+ polyarthritis in a female adolescent already suffering from DM1 and Hashimoto's thyroiditis successfully treated with etanercept.

This case report studied a teenage girl that was diagnosed with DM1 early in life and later with Hashimoto's disease, which may suggest genetic susceptibility in T-lymphocytes activation and might be related to other immune diseases.

She later developed an ANA+ and RF+ JIA which resulted unresponsive to MTX and was started on anti-TNF (etanercept) therapy followed by arthritis and diabetes control, lowering Glycated haemoglobin (HbAc1) levels and insulin doses. Immunotherapy aims to prevent autoimmune phenomena's onset in subjects at risk. Furthermore, immunotherapy inhibits pathogenic cells and stimulates alternative pathways helping suppress T-cell proliferation and cytokines. These cytokines are present in beta-cells destruction. Some studies showed that anti-TNF therapy can prevent this event.

Other case reports suggested that anti-TNFs, specifically etanercept, could be the starting point to diabetes' onset in patients already suffering from JIA. Although as it is now known both diseases can coexist, etanercept's role remains uncertain.

Confirmation and Identification of Biomarkers Implicating Environmental Triggers in the Pathogenesis of DM1.

Collaborative case-control study. 63 children total. It measured genetic and environmental variables and their influence in DM1 development. Blood was drawn and analysed for several parameters. The ones relevant for our review were mainly cytokines.

Cytokines responsible for cellular activation control and inflammation where found elevated in patients suffering from DM1, such as IL-17A, IL-18 and IL-7, however, TNF-alpha was unable to be detected in either group. IL-18 was one of the more abundant interleukins. Nevertheless, higher IL-18 levels were not found when control and DM1 patients were compared, providing no evidence of specific immune response.

The results show an overall lack of unique cytokine response specific to DM1 patients.

However, they show that whereas their study did not show TNF-alpha levels raised, there were others that did find lower, higher, and even cytokine levels. Nonetheless, IL-18 was shown to be measurable in most patients however not raised. Il-18 has been associated with hyperglycaemia.

Although this study cannot conclude if circulating interleukins higher levels in DM1 is the reason or a threat factor contributing to its development, CD4+ levels and IL-18 inhibitor levels are the most significantly sturdy. As they are produced by monocytes and macrophages, these elevations could suggest higher monocyte and inflammation cells activation.

Cytokine profile in patients with chronic non-bacterial osteomyelitis, juvenile idiopathic arthritis, and insulin-dependent diabetes mellitus.

In this study there were 42 children included, and cytokine levels were measured in non-bacterial osteomyelitis (CNO), JIA, and DM1 patients and healthy controls.

Important cytokines for our study were measured by ELISA: S100A8/A9 protein, ILs 4, 17, 18 and 1 and TNF-alpha.

CNO patients had higher interleukin levels than controls and DM1 patients, nevertheless, TNF-alpha and S100A8/A9 protein levels were higher in JIA patients which can help discriminate between CNO, JIA and healthy patients.

Therefore, increased level of proinflammatory cytokines, present not only in CNO, can play a significant role in monocyte activation and inflammation, and may prove to be valuable biomarkers and potential treatment targets of immune diseases.

S100 proteins, cytokines, and chemokines as tear biomarkers in children with juvenile idiopathic arthritis-associated uveitis

In this study tears were used to measure biomarkers as a not invasive technique. JIA and control patients were selected. S100A8/A9 was determined by ELISA, other cytokines such as IL-2, 18, 8 and TNF-gamma where also determined. When these biomarkers where undetectable in 40% of the samples, they were excluded from further evaluation. Comparing control and patients suffering from JIA related uveitis, there was no statistically significant differences between S100A8/A9 levels. However, in children with JIA related uveitis S100A12 was increased in active uveitis compared no inactive. Comparing uveitis by their activity rate, active uveitis patients had higher S100A12 protein and IL-8 levels. Therefore, these inflammatory biomarkers may help distinguish uveitis based on activity.

S100A12 protein and IL-8 are both associated with neutrophils. Being present in uveitis, they may suggest neutrophil activation and cytokine production resulting in autoimmune mediated uveitis. S100 and ILs roles need further investigation.

A clinical prediction model for estimating the risk of developing uveitis in patients with JIA.

A cohort study that tried to stablish risk factor for uveitis when already having a JIA diagnosis.

Children who developed uveitis were observed for a longer period, were younger, and were more frequently HLA-B27+, in addition, most patients with autoimmune uveitis were also ANA+, seronegative patients where the second ones more affected.

The use of anti-IL treatment was found to be lower in those patients that developed uveitis. On the contrary, the use of Anti-TNF therapy was found to be higher in the uveitis patients than in those without.

Although HLA-B27 and ANA positive patients were shown to develop uveitis more often, they were not found to be helpful to stablish uveitis risk due to their non specificity, as they are present in a big percentage of the general population. So, even if HLA-B27 is frequently related to anterior uveitis, its presence on the general population makes them not helpful for discrimination in JIA patients at risk of developing uveitis.

Undifferentiated arthritis was not associated with a decreased chance of uveitis commencement compared to oligoarthritis, this could be due to patients with undifferentiated arthritis in this cohort be positive for ANA and HLA-B27.

Epidemiology of paediatric uveitis and associated systemic diseases.

This was a retrospective observational study based in Korea. It included 155 patients. Apart from idiopathic uveitis, immune related diseases were the second cause of uveitis development. The five most common immune-mediated diseases related to uveitis were: JIA 14.8%, Behçet disease 6.5%, Kawasaki disease 1.9%, Vogt–Koyanagi–Harada syndrome1.9% and tubulo-intestinal nephritis1.3%. Furthermore, JIA accounted for 45.5% of all the systemic cases. Unilateral and anterior uveitis was the most common anatomical form. Those with uveitis associated with inflammatory illnesses had a significantly higher rate of systemic therapy.

As in the previous study, HLA-B27 and ANA levels were higher among patients with JIA related uveitis than on those with idiopathic uveitis. ANA are known to be related to paediatric uveitis as reactivity to histones has been reported in JIA related uveitis more frequently than on those affected solely by JIA.

Although there is limited evidence on genetic susceptibility to uveitis in JIA patients, HLA-B27+ patients are known to be associated with acute anterior uveitis and ankylosing spondylitis development.

They concluded that higher volumes of HLA-B27 and ANA were commonly related to JIA-uveitis, however, not in idiopathic arthritis.

Children in Korea with uveitis have a 33% chance of having un underlying immune disease, being JIA the most common.

Chronic and recurrent non-infectious paediatric-onset uveitis: a French cohort.

Descriptive, retrospective and bicentric study in which 147 patients with uveitis were identified either.

Again, the most common diagnosis was JIA associated to uveitis. This time, they were mostly bilateral and anterior. When related to JIA they were mostly ANA+. The study showed that a high proportion of patients achieved an inactive state of their uveitis after MTX treatment or biologic therapy. There were more complications in ANA+ patients, which is accompanies the difficulty for early diagnosis, stablishing the need of further investigation in prompt diagnosis. Disease-modifying antirheumatic drugs (DMARDs), especially anti-TNF-alpha antibodies showed better results in most cases and can prevent visual impairment. Patients treated since initial stages of their immune disease, had fewer visual complications and better visual prognosis.

Longer follow-up visits are needed to confirm long-term efficiency and safety of systemic treatments.

Effect of Lipopolysaccharides (LPS) on cytokine secretion from peripheral blood monocytes in JIA-associated uveitis patients with positive ANA.

In this study monocytes, TNF-alpha and IL-6 peaks were measured 6h after LPS stimulation. Surprisingly, ANA titles decreased after ocular inflammation control.

TNF-alpha and IL-6 increased rapidly in all groups and decreased after the 6-hour peak. The ANA+ group's cytokines raise suggest a strong response to LPS, whereas the ANA- group had a slower response and the control group had a flat response.

They also found that TLR4 signals on macrophages play a significant role on the development of acute uveitis.

JIA usually occurs due to destroyed immune self-tolerance. Systemic JIA is usually related to innate immunodeficiency. Once again, relationship between MHC class II and JIA was found, as CD4+ helper cells may carry a crucial role. Synovial fluid in JIA patients with inflamed joints manifested higher levels of Th17, associated with arthritis' severity.

As seen in previous studies, this one showed that younger age and ANA+ patients where risk factors for developing uveitis. However, they stablished that ANA is not believed to be a specific marker for uveitis in JIA patients.

Although the ANA+ group had a higher ratio of cells which may result in increased sensitivity to LPS, stimulation and activation of antigen-presenting cells in iris tissue, the specific mechanism has not been revealed this far, therefore it remains a goal for future research.

Risk factors and biomarkers for the occurrence of uveitis in JIA

This prospective, controlled, observational, multicentre study analysed 954 JIA patients. 133 developed uveitis, being female, early age of JIA onset, oligoarthritis JIA and ANA+ significantly associated with uveitis' outbreak. The influence of systemic treatment was evaluated in 898 patients. MTX was appeared to reduce risk of uveitis commencement.

In addition, S100A12 mean levels where similar in patients without uveitis and those that in follow-up visits presented the condition. Although S100A12 protein was associated with

higher risk of uveitis in other studies, it did not show a significant association in this article with uveitis onset.

Identifying patients at risk of developing uveitis is key, especially in those JIA groups in which uveitis is an important manifestation that could go unnoticed.

Uveitis related complications did not differ in sex, ANA positivity, JIA category and age of genesis. Patients treated with DMARDs such as MTX or biologic DMARDs before uveitis onset, had slightly fewer uveitis-related complications at first uveitis registration.

Uveitis manifestations in JIA affected children can often be initially asymptomatic and may lead to irreversible eye damage, therefore, identifying children with risk factors rapidly is crucial.

A lower risk of uveitis within JIA patients was found for HLA-B27+ children whilst HLA-B27 can be found in uveitis as well.

Besides, children receiving conventional, synthetic or biologic DMARDs had a significantly lower risk of uveitis onset.

Clinical characteristics and genetic analysis of A20 haploinsufficiency (HA20)

These cases report analysed three children with HA20, medical history and time to diagnosis where some of the parameters collected. Observational indices included clinical presentation, laboratory tests and aggressive evaluations were run, including genetic analysis. Not all patients showed the same results, differences in presentation were significant.

The first girl had an aggressive ANA- arthritis which was later found to be HA20 insufficient and was successfully treated with Infliximab. The second girl was diagnosed with active spondylitis and the Magnetic resonance imaging (MRI) displayed indicia of inflammatory changes. HLA-B27 blood levels were positive and was later diagnosed with JIA and started on sulfasalazine. However, inflammatory exacerbations happened and was later diagnosed with HA20, and infliximab treatment was commenced resulting successful. The last child had recurrent fever with ANA- blood levels and HA20 insufficiency in genetic scrutiny later

treated with hormone and thalidomide immunosuppressive medication, stabilizing the disease.

HA20 is a genetic mutation in TNF-alpha induced protein 3 gene, resulting in negative feedback inhibition of NF-kB, a family of proteins. When activated by TNF B cell activating factors and others, can induce chemokine production and participate in inflammatory processes. When inhibition is supressed, persistent inflammatory response is initiated inducing immune diseases such as SLE, JIA, Hashimoto's disease amongst others. Laboratory examinations may show autoantibodies presence. The treatment's axis is based on patients' phenotypes. In our patient's, biologic and immunosuppressive medicaments were satisfactory.

Improvement in genetic evaluation and technology have led to better and earlier diagnosis of immune diseases caused by single-gene mutations, as well as treatment plans that have ushered better outcomes.

Associations of lymphocyte subpopulations with clinical phenotypes and long-term outcomes in juvenile-onset systemic lupus erythematosus (SLE).

Children were assessed for different lymphocyte subpopulations levels and related to different phenotypes. The γ, δ T cells high group and NK cells high set were significantly related to higher frequency of mucosal ulcer, and the $CD4^+$ T cells high group was significantly associated with higher rate of arthritis. Tests showed that an imbalance in lymphocyte subtypes participated in immune response in SLE patients, leading to inflammatory reaction contribution through Interferon (IFN) I, II and NK cells that produce cytokines in charge of T cells, B cells and NK cells regulation.

Not all LSE patients have the expected response to B cell targeted therapy, which may entail that immune cell disfunction is not specific to B cells. γ δ T cells and NK cells were related to oral ulcers, CD8+ cells with vasculitis and CD4+ cells, as previously started, with arthritis. Therefore, therapies regarding these cells may show promising results in LSE patients. Changes in lymphocyte subtype were demonstrated to be associated with different phenotypes which could help with personalised treatment.

Perinatal risk factors for paediatric onset DM1, autoimmune thyroiditis, JIA, and inflammatory bowel diseases.

The evidence of early age autoimmune diseases has increased significantly in the past years. This Register-based cohort study, made in Finland, aims to first describe simultaneous prevalence of autoimmune diseases in teens and perinatal risk factors to plan effective and preventive treatment strategies.

Teens were recruited mostly in school; 11.407 children were selected. The risk for developing JIA, DM1, thyroiditis, and inflammatory bowel disease was studied linking it to the cohort of three national health registries. 2,1% of the recruited teenager obtained the diagnoses above. Having preterm births and postnatal antibiotics use was found to be more related to immune illness development. The evidence of this diseases has grown notably in the past years. Nevertheless, preterm birth was not related to a specific immune disfunction and has been repeatedly reported to have some correlation with DM1, JIA, and autoimmune thyroiditis' development, making it plausible to be not only related to one disease but a conglomerate.

An interconnection between preterm birth and postnatal antibiotics compared to full term children and non-antibiotic users can be found which may lead to deprivation of antibodies development. Furthermore, preterm births may prevent children from obtaining intrauterine antibodies from the female progenitor. Altogether, susceptibility to autoimmune disease may be feasible. However, contrary to likely beliefs, caesarean births were not found to be related to higher risk of autoimmune diseases. Although preterm children born via C-section received more postnatal antibiotics (ATB) than those delivered vaginaly, this use of ATB seems more linked to autoimmune conditions outbreak than the caesarean itself.

It remains uncertain if these findings are casual or extended beyond. Further studies on microbiota in diagnosis of autoimmune disease must be carried to rule out coincidence.

Reactive arthritis (RA) and undifferentiated peripheral spondylarthritis (UPSA) share HLA-B27 subtypes and serum and synovial fluid cytokine profiles.

Two cohorts were analysed with the purpose to stablish if reactive arthritis, also known as Reiter's syndrome (RS), affected children and undifferentiated peripheral spondylarthritis (UPSA) suffering kids had differences in HLA-B27 subtypes or cytokine profiles. In cohort I HLA-B27 was present in over 80% of RS and UPSA patients, being the B*2705 subtype the most common in both. However, discrepancies between other studies related to this matter have been manifested. Although HLA-B27 prevalence has being widely studied, data is still limited.

In cohort II, cytokines were measured in synovial fluid and serum, finding no differences between the two groups. A comparison between chronic and acute RS showed lower levels of TNF-α and increased levels of IL-6, IL-17 in chronic patients. TNF-α was also found to be higher in children suffering from UPSA or RS compared to healthy controls. No differences in HLA-B27 were found in either group. HLA-B27 and chemokine associations have been discovered in both conditions. Similarities in HLA-B27 subtypes and cytokine profiles have been described with previous studies showing comparable results.

Trajectories of disease courses in the inception cohort of newly diagnosed patients with JIA: the potential of serum biomarkers at baseline.

Biomarker levels were highly variable between patients with different JIA categories. Several biomarkers such as: IL-18, S100A8/A9 and S100A12 proteins were elevated in systemic JIA when compared to other categories. Baseline cytokines levels were higher in patients suffering from oligoarthritis even though the extended kind would be expected to have higher inflammatory activity. Therapy with systemic glucocorticoids in a higher proportion prior to blood sampling could explain this. When contrasted with healthy controls, serum biomarkers were substantially raised in JIA patients altogether.

Higher rates of S100A8/A9 proteins were observed in those treated with disease modifying drugs, making them biomarkers for children in need of biologic treatment. This divergences from other studies which showed that S100A8/A9 proteins higher levels had a better response to MTX.

A few biomarkers have also demonstrated an ability to inform of the disease's trajectory, activity, and outcome. Drug-naïve patients had higher levels of IL-6, IL-17 and TNF-α, which may indicate Th17 enhanced activity. Il-6 is a crucial cytokine in Th17 promotion in cell differentiation and inhibition of regulatory T cells induction. Th17 can express TNF-α when fully differentiated, promoting inflammatory activation of antigen-presenting cells. The same happens with IL-17 in which activation of target cells can activate cells and recruit to inflammation sites.

Therefore, patients with active JIA have a greater association with an increased inflammation degree in preliminary stages of the condition, appearing to be associated with severe and persistent form of the disease. This supports the theory that extended inflammation presence could translate into immune changes affecting long-term course, nevertheless, further studies are needed.

Juvenile spondylarthritis in the childhood arthritis and rheumatology research alliance registry: high biologic use, low prevalence of HLA-B27, and equal sex representation in sacroiliitis

Case report of childhood arthritis. Over 900 children with ERA or juvenile psoriasic arthritis (JPA) were studied. As expected, differences were noticed, children with ERA were older at initial diagnosis and more likely to be HLA-B27+. In both conditions a bast majority of children had a polyarticular affectation at some point, most on biologic treatment, this could be influenced by registry entry criteria.

Biologic treatment was greater amongst those with sacroiliitis; however, this is not surprising as DMARDs are usually ineffective in patients affected of axial disease. Contrary to other studies HLA-B27 was present in a lower percentage of patients, being possibly influenced by the mix of JPA and ERA patients. Describing phenotypes is the first step towards pathophysiology understanding and orientating optimal treatments.

After reading and summarizing all the articles included in this review, a table with a personal summary was done and is shown below:

Table 8. Self-made summary table

Article	Summary
29	Being Etanercept a TNF inhibitor that reduces inflammation and immune response, suppression of development of other immune diseases might happen when etanercept is used. Making a common immune pathway plausible.
30	IL-18 is not only present in JIA but other immune diseases the patients suffered. Therefore, underlying relationship between inflammation and autoimmunity in JIA and other immune diseases might happen. The fact that Etanercept was useful for the three immune diseases, also enforces the theory that JIA and other immune diseases share immune pathogenesis.
31	The relationship between proinflammatory cytokines, present in plasma of immune diseases included in the article, are present in higher levels when compared to the control group. Some correlation in their pathogenesis and the possibility of finding several immune diseases in the same patient is reasonable.
32	S100 proteins elevation in patients with active immune uveitis and JIA are increased, as well as IL-8 which may agree with our theory that immune diseases are related and can be more prone to develop in those already ill.
33	HLA-B27 has not been demonstrated to be useful for predicting uveitis onset, due to biased interpretation, the same happens with ANA positive patients. This shows that although many times immune bases could be related, not always they have to be. HLA-B27 and ANA are unspecific markers present on the general population.
34	Although HLA-B27 and ANA are present in many healthy children, their positivity in JIA has shown a connection with uveitis development. Their role

	remains unknown, and its presence does not necessarily mean uveitis onset. Further studies need to be conducted on this topic.
35	Early uveitis treatment showed fewer visual complications and better prognosis. When referring to our objectives this may be due to common molecular bases for both JIA and uveitis, making it possible to treat JIA and interfere in uveitis' inflammatory cascade, resulting in uveitis control and better outcome.
36	Higher ANA+ patients in relationship with higher ratio of IL-6 and TNF peak suggests a higher activation of antigen-presenting cells followed by inflammation. These results may show parallel pathways in JIA and immune uveitis related with TH17.
37	HLA–B27 positivity in uveitis has been described previously, therefore, these negative results may be contradictory. Children receiving DMARDs had a significantly lower risk of uveitis emergence. Once again, this could orientate us towards possible common immunological pathways.
38	HA20 is related to numerous autoimmune diseases of interest. This mutation can affect TNF-alpha inducing NK-kB proteins and inflammation cascade activation. The fact that infliximab is useful for HA20, and its derived diseases makes it, a plausible option to have common immune system alterations.
39	Cytokines produced in SLE are typically those commonly found in JIA which could lead to a possible interrelation of both diseases and maybe a higher possibility to develop both at the same time. CD4+ cells usually related with arthritis may produce a cytokine cascade in SLE patients, also present in JIA.
40	Preterm delivery and postnatal antibiotics could prevent new-borns to develop a healthy immune system which can lead to defective immunity.

41	As we have seen in the past articles, HLA-B27 and IL-6 are especially important yet not determining factors in development of immune conditions. However, its presence will increase the risk of developing any of these diseases.
42	Proteins such as S100A8/A9 are higher in JIA patients. The presence of this biomarkers has been manifested to also relate to other autoimmune diseases.
43	HLA-B27 was described to be positive in fewer cases. This could be due to registry entry criteria. This is not conclusive and reinforces the idea that further investigation needs to be carried.

6. Discussion

When we first started this systematic review, we asked ourselves if JIA had underlying molecular bases related to other immune diseases, that could make children more prone to developing other conditions. Likewise, we wanted to observe if there was any evidence that early diagnosis and treatment prevented commencement of other immune illnesses and their outcomes.

The data retrieved from these articles was not conclusive, as there are differences in results in various papers. However, some similarities have appeared, which would help orientate results towards our hypothesis.

Although not referring to molecular bases, one article showed that preterm birth and new-born use of antibiotics had a greater chance of developing immune diseases (40), this could inhibit children to develop healthy and strong autoimmune systems which could lead to self-attacking cells or immune cell dysregulation leading to long-term inflammation and autoimmunity intolerance followed by immune diseases onset.

Furthermore, the paper that investigated HA20 (38) showed that mutation and dysregulation of genetic material can lead to immunity disfunction, which leads to TNF-α mutations. This may alter cytokine production inhibition, opening to overwhelming inflammatory response, persistent inflammation, inflammatory cell recruitment and therefore, autoimmune condition starting point.

The main objective fact that is important to mention, is that there are no such thing as specific biomarkers for these diseases. As we have seen in most articles, there are biomarkers such as S100 proteins or mutual cytokine activation (IL-17, IL-18, IL-6) that are present in a variety of autoimmune conditions which could be related to an underlying pathogenesis.

Moreover, HLA-B27+ and ANA+ patients were shown to be generally more affected by immune conditions that those who didn't in 26,67% articles (33,35,36,41). These, however, are widely known to not be specific prediction markers for autoimmune diseases outbreak, as they are present in a high percentage of the general population. Therefore, although they are shown to have some kind of relationship with immune diseases, further research need to

be conducted in genetic areas to stablish undercover mutations that could lead to autoimmune illnesses debut.

Nevertheless, ANA+ JIA patients showed higher reaction to LPS stimulation in one article (36), which showed higher response of the autoimmune system and uveitis onset, making it credible to have an underlying mutual pathway or chemokine activation.

In addition, HLA-B27 positivity, although it is known to be present in most patients suffering from different autoimmune conditions, showed a uveitis' onset risk reduction after being diagnosed with JIA in one article. Significance cannot be assured, as just one study, (which had recruitment and sample size limitations), showed HLA-B27 to reduce its risk (37).

Besides, other article (43) surprisingly showed that spondylarthritis affected patients had a lower rate of HLA-B27 positive children which can be due to inclusion or exclusion criteria or even from the lack of patients.

When focusing on S100 proteins we can see that different studies stablish different things and are not only inconclusive but contradictory. While one article stablishes higher rates of S100A8/A9 proteins in JIA patients (31), other article displays that there is no difference between control patients and ill patients making them non dependable and useless as an agreement has not been reached yet (32). 20% of the studies also talk about S100A12 proteins, which are present in different autoimmune diseases, these, were found to be elevated consistently in patients with active uveitis with underlying JIA and could be useful when classifying uveitis activity in affected children (37). Furthermore, S100A12 are neutrophil regulators that, when damaged they can perpetuate cytokine activation. However, in other study S100A12 did not show a difference in serum levels between non-uveitis patients and those suffering from active uveitis in follow-up visits (37). Nevertheless, both S100A8/A9 and S100A12 were found in other paper to be present in patients suffering from systemic JIA but not uveitis. S100A8/A9+ patients were also found to have a higher need of biologic treatment in contrast with other articles that showed better response to MTX (42). This makes S100 proteins unreliable when determining undercover common pathways in immune diseases as contradictions in different articles are multiple.

When talking about interleukins, 40% of the papers referred about them. IL-18 was found to be elevated in one patient suffering from diverse autoimmune diseases, as well as IL-17A and IL-7, which could lead to inflammation and further condition development (30). In addition, a lack of specific chemokine response was described. However, other study showed lower cytokine levels in DM1 patients when compared to CNO suffering patients (31), however, higher than in control patients. ILs levels were considered to have an underlying significant role in both conditions. Furthermore, other studies (32,36) showed increased levels of IL-8 and IL-6 peaking at the 6-hour mark after LPS stimulation. IL-8 is known to have neutrophil implication, leading to inflammation which could help discern between active immune mediated uveitis and uveitis from other etiologies.

Again, IL-6 was found to be elevated as well as IL-17 in RS patients (41), and although not the same, similar cytokine profiles were also found in peripheral spondylarthritis. Lastly, IL-18 levels were found higher in systemic JIA compared to other subtypes. Nevertheless, drug-naïve patients had elevated levels of IL-6 and IL-17. IL-6 plays a crucial role in Th17 promotion and inhibition of regulatory T cells, which can lead to TNF-α expression and inflammation promotion, it yet has not been found to be determinant. All of this, although it seems coincidence, it could have intrinsic immune pathways that, when activated, could make immune patients more prone to suffer from different conditions. Even though several studies show increased levels of the same cytokines in different immune diseases, the relation between one another needs to be further investigated. Yet an underlying connection seems plausible. One topic was constant in all these articles, ILs are known to participate in inflammation cascade activation, when dysregulated, it could perpetuate inflammation and disease development playing a vital role on these diseases and proving to be valuable biomarkers.

TNF-α was another recurrent topic when reviewing articles, being mentioned in 40% of the mentioned papers. Although it was not shown to be elevated, but unable to be detected in controls or DM1 in one article (30), other articles showed a peaks after LPS stimulation in uveitis related to JIA and an association with HA20 (36), which can lead to negative feedback inhibition of NF-kB leading B cell and interleukin proliferation, causing

inflammation, that, when persistent, can induce different autoimmune diseases (38). Moreover, higher levels in acute RS and UPSA were determined when compared to controls. However, chronic patients had lower levels of TNF-α, this could be due to the chronic characteristic of inflammation activation. Drug-naïve JIA patients (43) were also discovered to have higher levels of TNF-α (which enhances TH17 activity and therefore inflammation), than patients on treatment. These raises in TNF-α levels in non-treated patients seems related to JIA medicaments' effects on inflammation.

One article (39), talked about the differences in lymphocyte subpopulation in SLE and its long-term outcomes. CD4+ raised levels were stablished to make patients to have higher odds of developing arthritis. Besides, an imbalance of lymphocyte subtypes altered immune response in LSE patients, leading to inflammatory response. Another study also referred to CD4+ helper cells (36) playing a key role in Th17 activation and therefore inflammation cascade in JIA patients. A last paper (30) also referred to CD4+ cells as a robust risk factor for DM1 development, making these three diseases related somehow.

Lastly, treatment effectiveness is crucial for immune diseases affected patients' quality of life. Our first article showed that etanercept, an anti-TNF-α drug was successful for treating not only JIA but also DM1 (29). Also, anti-TNF treatment showed to be more prevalent in those suffering from immune uveitis and JIA being useful to improve uveitis commencement and prevention of visual impairment, as well as helping with JIA (33,35). Additionally, MTX showed a lower risk for autoimmune uveitis and other complications on JIA patients already receiving therapy (37). Monoclonal antibodies (43), such as Infliximab (38), showed success when treating JIA, spondylarthritis and sacroiliitis. This high rate of positive results on several immune diseases makes it important to investigate on this area regarding therapy targets.

Papers regarding this topic are limited as we have seen, and study limitations are numerous, making it even harder to study these correlations. They were also conducted in different countries with different validity standards. Conclusions that were met are displayed below.

7. Conclusions

In this systematic review fifteen articles were reviewed, focusing on finding a correlation between JIA molecular bases and other immune diseases. The quality of the papers was not ideal due to generally small sample sizes in different diseases. Evidence reviewed, has yet not stablished a direct correlation between JIA molecular bases and other immune diseases being more prone to initiate when already suffering JIA. Although it seems plausible to assume there might be a correlation.

The following conclusions were met:

1.- Most autoimmune diseases discussed showed an outstanding response to either MTX or other DMARDs which relates different immune diseases although not an agreement has been reached.

2.- There is not enough information nor investigation regarding this topic, therefore, further research in this topic must be carried to stablish sturdy correlations that help prevent immune disease onset specially in children, improving their quality of life by ensuring early diagnosis and treatment.

3.- Unfortunately, there was no evidence found that correlated immune molecular bases to underdiagnosis of these immune mediated diseases, so the reason of this conditions' underdiagnosis remains unknown.

8. Acknowledgments

First and foremost, I would like to thank Dr Ventura for his expert advice and encouragement throughout this project.

Furthermore, I would like to thank my outstandingly supportive family, but specially my mum for always believing in me and never letting me give up. Thanks to my brothers too, without them, studying at home wouldn't have been as interesting and fun as it was with their loud, yet amusing personalities. Without any of you I wouldn't be here today. Thank you.

9. Bibliography

1.- Juvenile rheumatoid arthritis [Internet]. Hopkinsmedicine.org. 2021 [quoted March 12th of 2023]. Available at: https://www.hopkinsmedicine.org/health/conditions-and-diseases/arthritis/juvenile-idiopathic-arthritis

2.- Artritis juvenil. Bones, Joints and Muscles [Internet]. 2002 [quoted March 12th of 2023]; Available at: https://medlineplus.gov/spanish/juvenilearthritis.html

3.- Juvenile idiopathic arthritis [Internet]. Medscape.com. 2022 [quoted March 12th of 2023]. Available at: https://emedicine.medscape.com/article/1007276-overview

4.- De Benedetti F, Schneider R. Systemic juvenile idiopathic arthritis. En: Textbook of Pediatric Rheumatology. Elsevier; 2011. p. 236–48.

5.- Researchgate.net. [quoted March 12th of 2023]. Available at: https://www.researchgate.net/publication/237562872_Juvenile_Idiopathic_Arthritis_in_Hong_Kong_and_Its_Current_Management

6.- Momah T, Ray L. Juvenile idiopathic arthritis: Old disease, new tactics. J Fam Pract [Internet]. 2019 [quoted March 12th of 2023];68(2):E8–13. Available at: https://www.mdedge.com/familymedicine/article/196058/rheumatology/juvenile-idiopathic-arthritis-old-disease-new-tactics

7.- Artritis idiopática juvenil [Internet]. Pediatría integral. 2017 [quoted March 12th of 2023]. Available at: https://www.pediatriaintegral.es/publicacion-2017-04/artritis-idiopatica-juvenil/

8.- Juvenile Idiopathic Arthritis [Internet]. Ada.com. [quoted March 12th of 2023]. Available at: https://ada.com/conditions/juvenile-idiopathic-arthritis/

9.- Shenoi S, Shaffer ML, Wallace CA. Environmental risk factors and early-life exposures in juvenile idiopathic arthritis: A case-control study. Arthritis Care Res (Hoboken) [Internet]. 2016;68(8):1186–94. Available at: http://dx.doi.org/10.1002/acr.22806

10.- Juvenile idiopathic arthritis [Internet]. Mayoclinic.org. 2022 [quoted March 12th of 2023]. Available at: https://www.mayoclinic.org/diseases-conditions/juvenile-idiopathic-arthritis/diagnosis-treatment/drc-20374088

11.- Rua Elorduy MJ. Nuevos tratamientos en la artritis idiopática juvenil [Internet]. Reumaped.es. [quoted March 12th of 2023]. Available at: https://reumaped.es/images/site/pdf/2002/nuevos_tratamiento_aij.pdf

12.- Artritis reumatoide [Internet]. Mayoclinic.org. 2023 [quoted March 12th of 2023]. Available at: https://www.mayoclinic.org/es-es/diseases-conditions/rheumatoid-arthritis/diagnosis-treatment/drc-20353653

13.- Treatment with adalimumabin amyloidosis secondary to rheumatoid arthritis Researchgate.net. [quoted March 12th of 2023]. Available at: https://www.researchgate.net/publication/235385766_Treatment_with_adalimumab_in_amyloidosis_secondary_to_rheumatoid_arthritis_Two_case_reports

14.- Juvenile idiopathic arthritis [Internet]. Cleveland Clinic. [citado el 4 de abril de 2023]. Disponible en: https://my.clevelandclinic.org/health/diseases/10370-juvenile-idiopathic-arthritis

15.- Cabiedes J, Núñez-Álvarez CA. Antinuclear antibodies. Reumatol Clín (Engl Ed) [Internet]. 2010 [quoted March 12th of 2023];6(4):224–30. Available at: https://www.reumatologiaclinica.org/es-antinuclear-antibodies-articulo-resumen-S2173574310700496

16.- The Editors of Encyclopedia Britannica. major histocompatibility complex. In: Encyclopedia Britannica. 2023.

17.- Idriss HT, Naismith JH. TNF alpha and the TNF receptor superfamily: structure-function relationship(s). Microsc Res Tech [Internet]. 2000 [quoted March 12th of 2023];50(3):184–95. Available at: https://pubmed.ncbi.nlm.nih.gov/10891884/

18.- Donato R, Cannon BR, Sorci G, Riuzzi F, Hsu K, Weber DJ, et al. Functions of S100 proteins. Curr Mol Med [Internet]. 2013 [quoted March 12th of 2023];13(1):24–57. Available at: http://dx.doi.org/10.2174/156652413804486214

19.- Xia C, Braunstein Z, Toomey AC, Zhong J, Rao X. S100 proteins as an important regulator of macrophage inflammation. Front Immunol [Internet]. 2017;8:1908. Available at: http://dx.doi.org/10.3389/fimmu.2017.01908ç

20.- Justiz Vaillant AA, Qurie A. Interleukin. StatPearls Publishing; 2022. [Internet]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK499840/

21.- Dinarello CA. The IL-1 family and inflammatory diseases. Clin Exp Rheumatol [Internet]. 2002 [quoted March 12th of 2023];20(5 Suppl 27): S1-13. Available at: https://pubmed.ncbi.nlm.nih.gov/14989423/

22.- Ankylosing spondylitis [Internet]. Mayo Clinic. 2023 [quoted March 12th of 2023]. Available at: https://www.mayoclinic.org/diseases-conditions/ankylosing-spondylitis/symptoms-causes/syc-20354808

23.- Systemic lupus erythematosus [Internet]. Medlineplus.gov. [quoted March 12th of 2023]. Available at: https://medlineplus.gov/ency/article/000435.html

24.- Mageed SA, Rawla P, Mahmoud MA, Shahba A. Systemic lupus erythematosus, hypoparathyroidism, and hemolytic anemia in a patient with Wilson's disease. Reumatologia [Internet]. 2019 [quoted March 12th of 2023];57(4):239–42. Available at: https://www.semanticscholar.org/paper/c4fb55d84a4c2182d8eabd7c389b287b1d985c1

25.- Amador-Patarroyo MJ, Peñaranda AC, Bernal MT. Autoimmune uveítis [Internet]. El Rosario University Press; 2013. Available at: https://www.ncbi.nlm.nih.gov/books/NBK459445/

26.- Type 1 diabetes [Internet]. Medlineplus.gov. [quoted March 12th of 2023]. Available at: https://medlineplus.gov/ency/article/000305.htm

27.- Hill Gaston JS. Reactive Arthritis. In: Kelley and Firestein's Textbook of Rheumatology. Elsevier; 2017. p. 2087–94. [Internet]. Available at: https://www.webmd.com/arthritis/arthritis-reactive-

arthritis#:~:text=Reactive%20arthritis%2C%20formerly%20referred%20to,the%20body)%2C%20and%20skin

28.- Hashimoto's disease [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases. NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases; 2022 [quoted March 12th of 2023Available at: https://www.niddk.nih.gov/health-information/endocrine-diseases/hashimotos-disease

29.- Olivieri AN, Iafusco D, Mellos A, Zanfardino A, Mauro A, Granato C, et al. Refractory rheumatoid factor positive polyarthritis in a female adolescent already suffering from type 1 diabetes mellitus and Hashimoto's thyroiditis successfully treated with etanercept. Ital J Pediatr [Internet]. 2013;39(1):64. Available at: http://dx.doi.org/10.1186/1824-7288-39-64

30.- Harms RZ, Ostlund KR, Cabrera MS, Edwards E, Fisher M, Sarvetnick N. Confirmation and identification of biomarkers implicating environmental triggers in the pathogenesis of type 1 diabetes. Front Immunol [Internet]. 2020;11:1922. Available at: http://dx.doi.org/10.3389/fimmu.2020.01922

31.- Kostik MM, Makhova MA, Maletin AS, Magomedova SM, Sorokina LS, Tsukasaki M, et al. Cytokine profile in patients with chronic non-bacterial osteomyelitis, juvenile idiopathic arthritis, and insulin-dependent diabetes mellitus. Cytokine [Internet]. 2021;143(155521):155521. Available at: http://dx.doi.org/10.1016/j.cyto.2021.155521

32.- Angeles-Han ST, Utz VM, Thornton S, Schulert G, Rodriguez-Smith J, Kauffman A, et al. S100 proteins, cytokines, and chemokines as tear biomarkers in children with juvenile idiopathic arthritis-associated uveitis. Ocul Immunol Inflamm [Internet]. 2021;29(7–8):1616–20. Available at: http://dx.doi.org/10.1080/09273948.2020.1758731

33.- Van Straalen JW, Giancane G, Amazrhar Y, Tzaribachev N, Lazar C, Uziel Y, et al. A clinical prediction model for estimating the risk of developing uveitis in patients with juvenile idiopathic arthritis. Rheumatology (Oxford) [Internet]. 2021;60(6):2896–905. Available at: http://dx.doi.org/10.1093/rheumatology/keaa733

34.- Shin Y, Kang J-M, Lee J, Lee CS, Lee SC, Ahn JG. Epidemiology of pediatric uveitis and associated systemic diseases. Pediatr Rheumatol Online J [Internet]. 2021;19(1):48. Available at: http://dx.doi.org/10.1186/s12969-021-00516-2

35.- Morelle G, Gueudry J, Uettwiller F, Wouters C, Bader-Meunier B, Robert MP, et al. Chronic and recurrent non-infectious paediatric-onset uveitis: a French cohort. RMD Open [Internet]. 2019;5(2):e000933. Available at: http://dx.doi.org/10.1136/rmdopen-2019-000933

36.- Wang J, Wu H, Liu X, Jia H, Lu H. Effect of LPS on cytokine secretion from peripheral blood monocytes in juvenile idiopathic arthritis-associated uveitis patients with positive antinuclear antibody. J Immunol Res [Internet]. 2021;2021:6691681. Available at: http://dx.doi.org/10.1155/2021/6691681

37.- Tappeiner C, Klotsche J, Sengler C, Niewerth M, Liedmann I, Walscheid K, et al. Risk factors and biomarkers for the occurrence of uveitis in juvenile idiopathic arthritis: Data from the inception cohort of newly diagnosed patients with juvenile idiopathic arthritis study. Arthritis Rheumatol [Internet]. 2018;70(10):1685–94. Available at: http://dx.doi.org/10.1002/art.40544

38.-Zhang D, Su G, Zhou Z, Lai J. Clinical characteristics and genetic analysis of A20 haploinsufficiency. Pediatr Rheumatol Online J [Internet]. 2021;19(1):75. Available at: http://dx.doi.org/10.1186/s12969-021-00558-6

39.- Lerkvaleekul B, Apiwattanakul N, Tangnararatchakit K, Jirapattananon N, Srisala S, Vilaiyuk S. Associations of lymphocyte subpopulations with clinical phenotypes and long-term outcomes in juvenile-onset systemic lupus erythematosus. PLoS One [Internet]. 2022;17(2): e0263536. Available at: http://dx.doi.org/10.1371/journal.pone.0263536

40.- Räisänen L, Viljakainen H, Sarkkola C, Kolho K-L. Perinatal risk factors for pediatric onset type 1 diabetes, autoimmune thyroiditis, juvenile idiopathic arthritis, and inflammatory bowel diseases. Eur J Pediatr [Internet]. 2021;180(7):2115–23. Available at: http://dx.doi.org/10.1007/s00431-021-03987-3

41.- Parida JR, Kumar S, Ahmed S, Chaurasia S, Mukherjee R, Singh R, et al. Reactive arthritis and undifferentiated peripheral spondyloarthritis share human leucocyte antigen B27 subtypes and serum and synovial fluid cytokine profiles. Rheumatology (Oxford) [Internet]. 2021;60(6):3004–11. Available at: http://dx.doi.org/10.1093/rheumatology/keaa746

42.- Ganeva M, Fuehner S, Kessel C, Klotsche J, Niewerth M, Minden K, et al. Trajectories of disease courses in the inception cohort of newly diagnosed patients with JIA (ICON-JIA): the potential of serum biomarkers at baseline. Pediatr Rheumatol Online J [Internet]. 2021;19(1):64. Available at: http://dx.doi.org/10.1186/s12969-021-00553-x

43.- Rumsey DG, Lougee A, Matsouaka R, Collier DH, Schanberg LE, Schenfeld J, et al. Juvenile spondyloarthritis in the Childhood Arthritis and Rheumatology Research Alliance registry: High biologic use, low prevalence of HLA-B27, and equal sex representation in

sacroiliitis. Arthritis Care Res (Hoboken) [Internet]. 2021;73(7):940–6. Available at: http://dx.doi.org/10.1002/acr.24537

The molecular basis of juvenile idiopathic arthritis and its correlation with other immune mediated diseases

Author: Gemma Clara Meira Blanco Tutor: Dr. Ignacio Ventura González

Introduction

JIA is currently the most common chronic rheumatic disease in children. It is known that it does not consist of a solely identity. Underdiagnosis is a barrier that puts stop to prompt treatment. We now know that other immune mediated diseases are carried by the same molecules as JIA and that they can coexist on the same patient, making relevant the investigation in this area.

Objectives

The main objective of this review is to try and stablish a relationship between Juvenile Idiopathic Arthritis's molecular bases and other immune mediated illnesses.

Methods

A systematic review focusing on immune molecules in different autoimmune conditions. Bibliographic research through: Medline, Google scholar and AEPED.

Results

15 articles dealing with different immune diseases and affected molecular bases form different countries were included and studied in this systematic review.

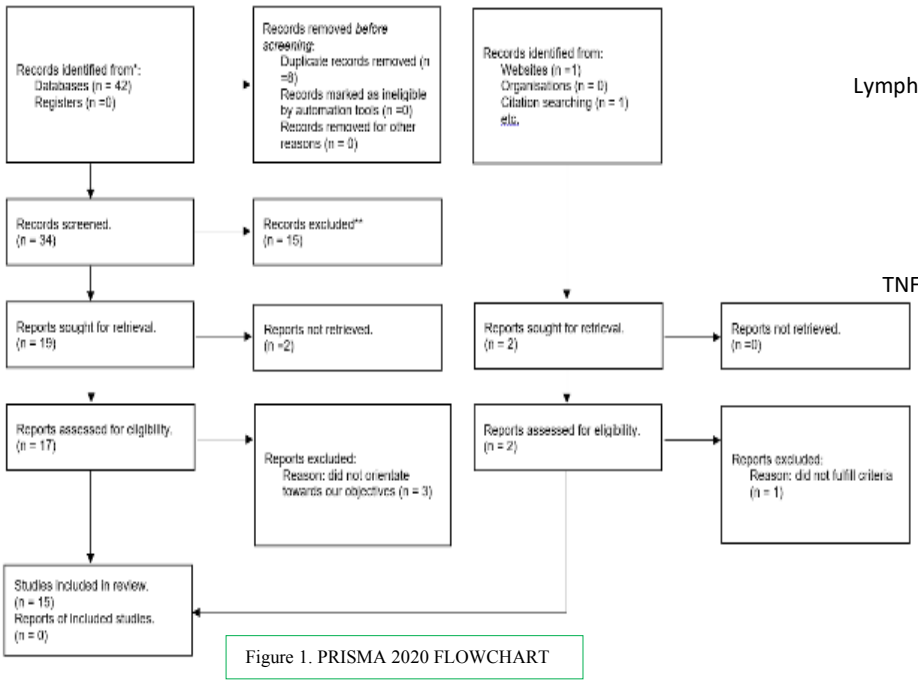


Figure 1. PRISMA 2020 FLOWCHART

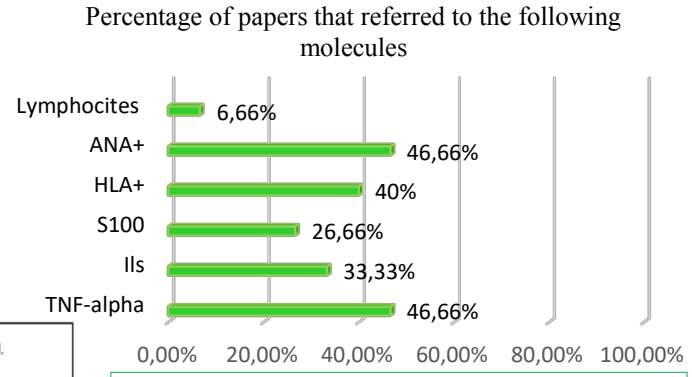


Figure 2. Percentage of papers that referred to the following molecules.

Conclusions

1.-Most autoimmune diseases discussed showed an outstanding response to either MTX or other DMARDs which relates different immune diseases. Not an agreement has been reached.

2.- There is not enough information nor investigation regarding this topic, therefore, further research in this topic must be carried to stablish sturdy correlations.

3.-Unfortunately, there was no evidence found that correlated immune molecular bases to underdiagnosis of these illnesses.

Bibliography

1.- Olivieri AN, Iafusco D, Mellos A, Zanfardino A, Mauro A, Granato C, et al. Refractory rheumatoid factor positive polyarthritis in a female adolescent already suffering from type 1 diabetes mellitus and Hashimoto's thyroiditis successfully treated with etanercept. Ital J Pediatr [Internet]. 2013;39(1):64. Available at: http://dx.doi.org/10.1186/1824-7288-39-64

2.- Ganeva M, Fuehner S, Kessel C, Klotsche J, Niewerth M, Minden K, et al. Trajectories of disease courses in the inception cohort of newly diagnosed patients with JIA (ICON-JIA): the potential of serum biomarkers at baseline. Pediatr Rheumatol Online J [Internet]. 2021;19(1):64. Available at: http://dx.doi.org/10.1186/s12969-021-00553-x

3.- Morelle G, Gueudry J, Uettwiller F, Wouters C, Bader-Meunier B, Robert MP, et al. Chronic and recurrent non-infectious paediatric-onset uveitis: a French cohort. RMD Open [Internet]. 2019;5(2):e000933. Available at: http://dx.doi.org/10.1136/rmdopen-2019-000933