

Advances in pediatric rheumatology

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The future of pediatric rheumatology is certainly exciting. Advances in classification and our knowledge of etiopathogenesis have opened new fields in the diagnosis and management of common and uncommon conditions. Until the mid-1980s, therapy for children with chronic arthritis consisted primarily of a small repertoire of anti-inflammatory drugs and corticosteroids. With the more advanced understanding of the immune system and the advent of biologic agents in the 21st century, pediatric rheumatologists now have many more therapies to offer patients, with the expectation that their disease will be controlled. Disorders that are more specific to pediatric patients, such as systemic-onset juvenile idiopathic arthritis, Kawasaki disease and autoinflammatory diseases, will be discussed in more detail in this article.

Pediatric rheumatology is a growing field. The number of young physicians devoted to this specialty is increasing, although some areas are still underserved even in developed countries. The aim of this article is to provide the opinion of the authors on what might be some important points to consider when thinking about the future of this speciality.

The article will focus on three important classes of childhood rheumatic diseases (periodic fever syndromes, systemic juvenile idiopathic arthritis [JIA] and Kawasaki disease), which have been chosen as they have the most possibility of advancement in the near future, and are also those in which the authors have the most experience.

Clinical issues

Diagnostic issues & classification

Diagnostic issues in pediatric rheumatic diseases remain a challenge despite the recent progresses in molecular biology that have enabled the confirmation of some clinical descriptions proposed in the past. Research is expanding more and more and it is expected that more will be known in the near future. Any progress in classification of pediatric rheumatic diseases relies on excellent clinical observations, which can then allow targeted research. An example of controversy in the field of pediatric rheumatology is the classification and nomenclature of juvenile arthritis. It was customary in the past to refer to this disease as a single entity characterized by the occurrence of chronic arthritis, and often to consider this disease as the equivalent of adult rheumatoid arthritis in children. However, in the late 1970s, two sets of criteria were proposed at the same time. A North American group of pediatric rheumatologists

applied the criteria known as the ACR criteria. At the EULAR conference on the Care of Rheumatic Children held in Oslo, Norway, it was proposed to label the disease as juvenile chronic arthritis, underlying that this disease was different from that of adult rheumatoid arthritis and establishing criteria for classification. Both sets defined age at onset as less than 16 years, and recognized three main subgroups at onset: systemic onset (with characteristic fever), polyarticular onset (with at least five inflamed joints) and oligoarticular onset (with a maximum of four inflamed joints). However, some discrepancies persisted for two to three decades, as mentioned in Table 1. The controversies were particularly recurrent for qualification of the disease as 'rheumatoid' or 'chronic'. To bridge the gap between both sides of the Atlantic, a solution was found at meetings of the Pediatric Rheumatology Committee of the International League of Associations of Rheumatologists, where a worldwide consensus was obtained for classification. It was agreed to name the disease JIA, and to define seven subgroups to achieve homogeneity within diseases and categories, as summarized in Box 1. One advantage of such classification criteria is that they make it easier to obtain more homogenous groups and to facilitate international exchanges and research. However, this type of classification might only be transient and will progress with the improving knowledge of the pathophysiological mechanisms of the disease. For example, in the near future, one might expect that the systemic type should be considered as a specific entity, as is the adult-onset Still's disease, which is not called 'systemic-onset rheumatoid arthritis'. Furthermore, this particular disease, in considering at least the

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Table 1. Comparison between the ACR and EULAR criteria for juvenile rheumatoid arthritis.

Characteristics	ACR	EULAR
Age at onset	Before 16th birthday	Before 16th birthday
Arthritis duration	At least 6 weeks	At least 3 months
Subtypes	Systemic Polyarticular Oligoarticular	Systemic Polyarticular Oligoarticular
Rheumatoid-factor positive	Included in juvenile rheumatoid arthritis	Excluded from juvenile chronic arthritis
Spondyloarthropathies	Excluded from juvenile rheumatoid arthritis	Included in juvenile chronic arthritis

extra-articular symptoms, is clinically very different from the other subgroups of JIA, and thus would be better considered as an autoinflammatory disease.

Acute rheumatic fever incidence has declined in industrialized countries for several decades but remains a public-health challenge in developing countries, where heart involvement is particularly frequent. In these countries, poverty and overcrowding remain a major cause of the occurrence of rheumatic fever. A large outbreak occurred in the mid-1980s in the USA in children from the upper and middle classes, underlying the fact that social factors are not always the cause. Furthermore, evidence of group A streptococcal infection was missing in a large proportion of these patients. Diagnostic guidelines for rheumatic fever known as the Jones criteria were updated in 1992 [1]. These guidelines still propose that streptococcal infection remains mandatory for diagnosis, which might be a problem for diagnosis in developed countries, where streptococcal infections are extremely common.

Molecular classification

Significant advances were recently made on the molecular mechanisms of some diseases. Identification of mutations is the best example of improvement in the knowledge of several diseases: they have been found in inflammatory disorders as well as in primary disorders of bone and connective tissues. Furthermore, a better understanding of the molecular mechanisms of some diseases will aid the development of effective therapies.

In chronic inflammatory diseases, phenotypically different syndromes can be identified by different mutations in a single gene. The best example is provided by the diseases associated with *CIAS1* mutations, which are called 'cryopyrinopathies' or cryopyrin-associated periodic syndromes. Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological

cutaneous articular (CINCA) syndrome (also called neonatal-onset multisystemic disease [NOMID]) were first recognized as separate entities. These cryopyrinopathies clinically share an urticarial-like rash and recurrent inflammation but differ greatly in severity – there is virtually no CNS or joint involvement in FCAS, while these are major manifestations of CINCA/NOMID [2]. The mildest condition, FCAS, most often has autosomal-dominant inheritance, whilst *de novo* mutations are generally observed in the severe type, referred to as CINCA/NOMID. The discovery of the genetic basis of cryopyrinopathies led to an understanding of the mechanism of inflammation mediated by IL-1, and to the proposal of a treatment by IL-1 inhibition, which induces a dramatic response in patients [3]. Similarly, mutations in the *NOD2* gene were found in Blau syndrome and Crohn's disease, two clinically very different disorders. Blau syndrome was described in families with symptoms including granulomatous arthritis, iritis and skin involvement, which may resemble early-onset sarcoidosis [4], while Crohn's disease is a chronic inflammatory bowel disease. The recent concept of 'nodosome' might open interesting insights into the molecular mechanisms by which *NOD2* can have a central role in the control of immune responses to bacterial infections and inflammation [5].

A proportion of disorders with indistinguishable clinical features of well-identified genetic syndromes lack mutations that can be searched for using conventional nucleotide sequencing. Patients with mosaicism of mutant *CIAS1* have recently been reported, raising the possibility that *CIAS1* mutations were overlooked in 'mutation-negative' patients owing to a low frequency of mosaicism. By collecting dying monocytes after lipopolysaccharide treatment, Japanese authors succeeded in enriching *CIAS1*-mutant monocytes and identifying low-level *CIAS1*-mosaicism in three out of four mutation-negative patients [6].

Box 1. International League of Associations for Rheumatology proposed classification criteria for juvenile idiopathic arthritis.

- Systemic arthritis
- Oligoarthritis
 - Persistent
 - Extended
- Polyarticular (rheumatoid-factor negative)
- Polyarticular (rheumatoid-factor positive)
- Psoriatic arthritis
- Enthesitis-related arthritis
- Undifferentiated
 - Fits no other category
 - Fits more than one category

Similar observations were reported in patients with recurrent inflammatory diseases with features of autoimmune lymphoproliferative syndrome, in whom lymphocytes had normal sensitivity to Fas-induced apoptosis *in vitro*. Heterozygous dominant *Fas* mutations were found in polyclonal double-negative T cells from the patients [7]. This type of research is very promising for syndromes with characteristic phenotypes in whom the genetic cause is unknown.

Clinical aspects

The clinical diagnosis of diseases in patients with unexplained recurrent or prolonged fever is now much easier owing to good clinical description backed up by genetic identification. Conversely, the knowledge of mutations allows the identification of atypical clinical aspects of the diseases. The main characteristics of these disorders are summarized in Table 2.

TNF-receptor-associated periodic syndrome (TRAPS [or familial Hibernian fever]), an autosomal-dominant condition caused by mutations in the *TNFRSF1A* gene, was first described in 1982 in an Irish family. This disease is characterized by recurrent attacks of fever, abdominal pain, synovial inflammation, rash, conjunctivitis and periorbital edema, typically lasting 1–4 weeks. However, atypical clinical features were identified as various mutations in the *TNFR1* gene were studied. Patients from various ancestries are known, including patients in populations of Mediterranean origin, which complicates clinically the differential diagnosis with familial Mediterranean fever (FMF). Age at onset varies

considerably from early infancy to late adulthood. The length of attacks can be less than 1 week. Abdominal pain is very frequent, but other symptoms, such as periorbital edema, can be missing. Isolated recurrent pericarditis has been described as the only clinical symptom. Anti-TNF therapy with etanercept has been used in TRAPS with good, but not optimal, results. The use of other anti-TNF agents, such as infliximab, seemed to induce exacerbation of the disease in one patient, while adalimumab has not yet been tested in TRAPS. These unexpected responses to different anti-TNF agents might reflect the complexity of the molecular/genetic mechanism responsible for TRAPS.

Diseases associated with mutations in the *CIAS1* gene encoding cryopyrin form a group of disorders with overlapping characteristics. As mentioned above, the mildest type, FCAS, is mostly characterized by recurrent, short and self-limited episodes of low-grade fever, rash and arthralgias occurring 1–2 h after cold triggering. The length of the attacks is usually short, less than 24 h. Most of the patients indicate a correlation between the severity of symptoms and the intensity of cold exposure. Early onset of the disease, at birth or within the first 6 months of age, is frequent, and a family history is often reported. MWS presents as recurrent episodes of fever, urticaria, joint and eye manifestations, deafness and renal amyloidosis in some patients. The course of the disease varies from typical recurrent attacks of inflammation to more permanent symptoms. Neurological involvement in MWS is unknown, although headache and papilledema have been reported in some cases. Sensorineural deafness is frequent (approximately 70% of cases) and begins usually in childhood or early adulthood. Amyloid A (AA) amyloidosis, due to chronic inflammation, is the main complication and develops in adulthood in approximately 25% of cases. CINCA/NOMID is the most severe phenotype in this spectrum of diseases. It was first described as a chronic inflammatory disease with rash, articular involvement and chronic aseptic meningitis. Fever is intermittent, and can be absent or very mild in some cases. Urticaria is usually present at birth or during the first months of life, and varies in intensity from patient to patient, with time and with disease activity. Bone and joint involvement vary in severity. In a third of patients, severe and disabling arthropathy caused by overgrowth of the patella and epiphyses of long bones occurs.

Table 2. Main clinical and genetic characteristics of the hereditary autoinflammatory disorders.

Clinical symptoms	TRAPS	FCAS	MWS	CINCA/NOMID	FMF	MVK deficiency	Behçet disease
Attack duration	>1 week	On cold exposure	2–3 days	Aleatory	1–3 days	3–7 days	3–6 days
Skin involvement	Migratory rash	Urticarial-like on cold exposure	Urticarial-like	Urticarial-like	Erysipeloid erythema	Urticarial-like erythema nodosum	Erythema nodosum, folliculitis, vasculitis
Lymph nodes/HSM	Splenomegaly	No	Rare	Yes	Splenomegaly	Painful cervical adenopathies	Not usual
Joint involvement	Arthralgia/arthritis	Arthralgia	Arthritis	Arthropathy	Arthralgia/arthritis	Arthritis	Arthritis
Serositis	Frequent	No	No	Rare	Abdominal pain very common	Rare	Rare
CNS involvement	No	No	Rare	Chronic meningitis, intracranial hypertension	No	No	Encephalomyelitis, aseptic meningitis
Hearing loss	No	No	Yes	Yes	No	No	No
Eye involvement	Conjunctivitis, periorbital edema	Conjunctivitis	Conjunctivitis, episcleritis	Papillitis, conjunctivitis, visual loss	Rare	Rare	Posterior uveitis, panuveitis, hypopyon, corneal ulceration
Amyloidosis	Possible	Rare	Yes	Yes	Frequent before colchicine	Rare	Rare
Genetic	AD	AD	AD	AD	AR	AR	
Chromosome	12p13	1q44	1q44	1q44	16p13.3	12q24	Unknown
Mutation	TNFRSF1A	CIAS1	CIAS1	CIAS1	MEFV	MVK	Unknown
Protein	55-kD TNF receptor	Cryopyrin	Cryopyrin	Cryopyrin	Marenostrin/pyrin	MVK	Unknown

AD: Autosomal dominant; AR: Autosomal recessive; CINCA: Chronic infantile neurological cutaneous articular; FCAS: Familial cold autoinflammatory syndrome; FMF: Familial Mediterranean fever; HSM: Hepatosplenomegaly; MVK: Mevalonate kinase; MWS: Muckle-Wells syndrome; NOMID: Neonatal-onset multisystemic disease; TRAPS: TNF-receptor-associated periodic syndrome.

Abnormalities of the CNS are present in almost all patients and are due to chronic aseptic meningitis with neutrophils infiltrating the cerebrospinal fluid. Cognitive impairment occurs in severely affected patients. Optic atrophy can develop; ocular manifestations can progress to blindness, and one patient in four has a significant ocular disability. Perceptive deafness is frequent, with onset during childhood or adulthood. AA amyloidosis develops with increasing age in some patients. These phenotypically very different diseases are caused by anomalies in the *CIAS1* gene, with some degree of genotype–phenotype correlation [2]. Few patients with FCAS or MWS and approximately 40% of patients with CINCA/NOMID are negative for *CIAS1* mutations, suggesting genetic heterogeneity. The mutations associated with cryopyrin-associated periodic syndromes result in spontaneous caspase-1 activation and excessive IL-1 β production, which suggests IL-1 β antagonism as a strategy for therapy. Treatment with IL-1 β antagonists, such as anakinra and, more recently, anti-IL-1 β monoclonal antibodies, has produced dramatic improvements in these three conditions.

FMF is the most common autoinflammatory syndrome, resulting from autosomal-recessive mutations in the *MEFV* gene, which encodes the pyrin/marenostrin protein. There are over 100 variants of the *MEFV* gene recorded to date, and most are disease-associated mutations. The three most commonly reported mutations are M694V, M680I and V726A. This disorder occurs most often among Sephardic Jewish, Arabs, Armenian and Turkish populations. Recurrent attacks of FMF last for 1–3 days and typically include fevers with inflammation of the pleural, pericardial and peritoneal linings. Characteristic erysipela-like erythema of the legs is another discriminatory feature, as is a family history consistent with autosomal-recessive inheritance. Persistent subclinical inflammation is observed between attacks in many FMF patients. A high incidence of AA amyloidosis, which usually presents with proteinuria, occurs in patients who do not receive effective colchicine therapy. Homozygosity for the M694V mutation predisposes patients to amyloidosis. There are no mutations in approximately 20–30% of patients with typical FMF features; in this case, the efficacy of colchicine therapy is a good argument for diagnosis. However, despite the efficacy of colchicine, amyloidosis remains an important cause of morbidity and

mortality in FMF owing to insufficient dosing, poor compliance and, in a small proportion of cases, a genuine lack of response.

Mevalonate kinase (MVK) deficiency, also known as hyper-IgD syndrome (HIDS), is an autosomal-recessive inherited syndrome first recognized in the early 1980s. It is caused by mutations in the *MVK* gene, resulting in deficient activity of the enzyme. In fact, this syndrome gathers together two rare entities: the mevalonic aciduria, which is well known to pediatricians, and the syndrome described as HIDS. Mevalonic aciduria is a rare inborn error of isoprenoid biosynthesis and is characterized by severe, periodic attacks of fever and inflammation, developmental delay, ataxia, and dysmorphic features. HIDS manifests in early childhood, often before the age of 6 months, and presents as attacks of fever of approximately 1-week duration, headaches, abdominal pain with diarrhea, lymphadenopathy, splenomegaly, cutaneous symptoms and joint manifestations. Attacks are often precipitated by external factors, such as immunizations or infections. The diagnosis is made by collecting urine during a febrile attack and measuring mevalonic acid excretion. Excretion is very high in newborns with severe disease, but it can be only mildly increased in children with milder forms. Furthermore, in children, the IgD dosage can be normal, which raises the question of the denomination of HIDS. When an increased excretion of mevalonic acid in urine is found, genetic proof of the disease can be confirmed. Most patients diagnosed with mevalonic aciduria have the MVK V377I variant due to the 1129G>A mutation in the *MVK* gene, along with the same or a different mutation in the second allele. The mechanisms by which abnormalities in MVK activity cause inflammation remain unclear. MVK is involved in cholesterol biosynthesis, but decreased cholesterol production is unlikely to drive the disease because cholesterol levels in MVK-deficient patients are in the low to normal range. Increased IgD levels might be unrelated to the disease, since IgD can be elevated in many other different conditions. Treatment is relatively ineffective; variable success has been obtained with the use of simvastatin and etanercept. A successful allogeneic bone marrow transplantation was recently performed in a child with a severe form, resulting in complete remission lasting for more than 1 year [8].

Behçet's disease (BD) probably represents an autosomal-dominant genetic condition favored by some environmental factors. It is observed from Japan to Turkey and the Middle East along

the 'Silk Route'. HLA B51 confers a significant risk of BD, particularly in patients with a family history of the disease. The *MICA* allele may confer additional risk. The disease presents as short attacks of 3–6 days with skin manifestations, such as erythema nodosum and folliculitis, headaches, and meningeal reaction (sometimes encephalitis). Recurrent oral ulcerations and genital ulcers are characteristic. Eye involvement is frequent in children with posterior uveitis, hypopion and severe uveitis, which can lead to blindness. Joint involvement with arthritis occurs in approximately 50% of the cases. The underlying lesion is a vasculitis. BD is difficult to treat: prednisone, thalidomide and colchicine were reported to help in some cases, and IFN- α associated with azathioprine has been beneficial in patients with eye lesions. Infliximab has also been an alternative in some patients with severe uveitis.

Research

Research is the base for advancement in all fields of science and medicine, and rheumatology is no exception. Recent advances in the elucidation of rheumatic-disease pathogenesis suggest that human autoimmune diseases, in general, do not result from single gene mutations, with the exception of some autoinflammatory disorders. Current knowledge suggests that a combination of genetic predisposition and environmental factors is needed in order for the full clinical disease to develop.

Numerous MHC and non-MHC linkages have been studied, and a substantial amount of work has gone into elucidating the non-HLA genetic associations in JIA [9]. Direct comparison of studies is difficult, since different ethnic populations, JIA subgroups, and systems of nomenclature and classification all impose limitations. Adding to the complexity is the polygenic nature of chronic childhood arthritis. It is extremely difficult to extrapolate definitive results of associations, which is probably because the disease is so heterogeneous in nature that numbers rarely reach statistical significance. However, the genome-wide association studies that have been performed up to now show that it will be possible to identify additional genetic determinants to those currently known.

Although we have no clues as to how to cure JIA, which is not a single disorder and of which we do not yet know the cause(s), research into its pathogenesis has resulted in new insights that might be therapeutically useful. For example, the idea that an infection (or vaccination) could lead

to a temporary release of self antigens, which, in combination with activation of innate immunity through Toll-like receptors, may lead to an enhanced proinflammatory immune response and to subsequent increased tissue damage, can open therapeutic perspectives by the regulation of immune responses against exogenous antigens.

In this regard, several studies have shown the importance of specialized subsets of T cells (regulatory T cells [Tregs]) in suppressing an ongoing T-cell response. For example, it has been demonstrated that reactivity of T cells to certain self antigens, such as heat shock protein (HSP)60, can induce Tregs that are able to ameliorate chronic inflammation [10]. It is likely that manipulations of such cell types *in vitro* and *in vivo* might lead to helpful therapeutic tools in the future; in fact, strategies have already been developed using HSP60 peptides to increase the number and function of Tregs [11–13].

Another area of interest and one that is gaining increasing attention is the emergence of biologic agents. TNF blockade represents a major breakthrough in the treatment of inflammatory arthritides, and therapeutic trials with the three TNF antagonists have shown their beneficial effects in polyarticular JIA [14–16]. However, response rate is nowhere near 100%, and we still need more precise early prognostic indicators that can enable us to decide when to start such treatments, which, although relatively well tolerated in the short term, are expensive and of which we do not yet know the long-term safety.

There is no evidence that simple determination of plasma TNF- α levels by ELISA allows such prediction for treatment with TNF- α inhibitors, although it is conceivable that patients producing high levels of TNF- α will be more sensitive to TNF- α inhibition. With functional cell-based assays, it might be possible to link response to the TNF inhibitor infliximab to the functional circulating level of TNF activity in plasma, since patients with high circulating levels of TNF activity (defined as the ability of rheumatoid arthritis synoviocytes to produce IL-6 in response to TNF- α) are more susceptible to respond to its inhibition [17]. It may be that genetic factors, such as cytokine gene polymorphisms, can play a role with respect to the clinical response to TNF inhibitors [18,19]. However, we have not been able to demonstrate such an effect when analyzing some IL-1 and TNF gene polymorphisms [20]. There are many more genetic factors that might play a role and that

deserve to be studied. Several of those relate to cytokine gene polymorphisms and have already been linked to the clinical response to anti-TNF in adult rheumatoid arthritis [21–23].

Genetic factors might also be important for response to other, more used second-line drugs, such as methotrexate, since variant alleles of several enzymes (e.g., thymidylate synthase and methylene tetrahydrofolate reductase) have been linked to its safety and/or efficacy [24]. The formation of a ‘pharmacogenetic index’ that incorporates the additive effect of multiple genetic variants on methotrexate efficacy and toxicity may enable the transition of methotrexate pharmacogenetic testing into the clinic.

Treatment

The major therapeutic advance in recent years has undoubtedly been the development of biologic agents, and their application for the treatment of pediatric rheumatic diseases. A very strong impetus for this has been the result of the so-called pediatric rule of the US FDA, which has been followed by similar actions from the corresponding European Medicines Evaluation Agency [25,26]. These regulations allowed pediatric rheumatologists to benefit from drug-company sponsorships and therefore enabled them to perform well-designed, controlled therapeutic trials. The multinational organization Pediatric Rheumatology International Trials Organization has been instrumental in this process and in the design and implementation of such trials.

Treatment protocols and controlled studies in JIA have been completed for cytokine inhibitors, including the three anti-TNF agents etanercept, infliximab and adalimumab, for the costimulator blocker abatacept (CTLA4-Ig) and for the IL-1 receptor antagonist anakinra [27,28]. Other studies on products such as a monoclonal anti-IL-1 antibody, the IL-1 trap rilonacept and the anti-IL-6 tocilizumab are underway, and new targeted drugs will become available as more detailed pathogenetic pathways are discovered.

The timing of medical treatment initiation with regards to its effectiveness is also a very important topic. A Phase IV, controlled, NIH-sponsored trial evaluating early aggressive drug therapy in polyarticular JIA is currently recruiting patients. The purpose of this study is to compare two aggressive drug regimens for children with polyarticular JIA by evaluating the proportion of participants who attain inactive disease after initial treatment with methotrexate plus placebo, or methotrexate plus etanercept plus

oral prednisolone. Specifically, the study will determine whether aggressive therapy initiated in the first 6 months of disease onset can result in inactive disease and clinical remission while on these medications.

A specific place within the family of childhood arthritides is occupied by systemic-onset disease (s)JIA, which represents up to 20% of all cases of JIA and which is quite uncommon in adulthood. This is quite a particular disease, well distinguished from the other forms of JIA both by its clinical features and by its pathogenesis and treatment. Since the therapeutic modalities available for sJIA have been limited, and these patients are prone to develop sudden and severe life-threatening drug-induced toxicity, the benefits of a given treatment must be balanced against the persistent and often permanently disabling nature of unremitting disease. Anti-TNF therapy offers limited benefit in sJIA patients, and inhibition of other cytokines, such as IL-1 or IL-6, could represent a mechanistically specific therapy for sJIA. In fact, IL-1 is an important mediator of this disease and anti-IL-1 agents are effective treatment [29]. However, lack of specificity of the initial systemic manifestations often leads to delays in diagnosis and initiation of therapy. Allantaz *et al.* analyzed leukocyte gene-expression profiles of pediatric sJIA patients and compared them with healthy controls and with subjects with other febrile illnesses [30]. They could identify genes differentially expressed in sJIA patients compared with healthy children, but these genes were also changed in patients with acute infections and systemic lupus erythematosus (SLE). An analysis of significance identified 12 genes that accurately classified an independent set of sJIA patients with systemic disease. Transcripts that changed significantly in patients undergoing IL-1 blockade were also identified. Thus, according to this study, signatures can be used to distinguish sJIA from other febrile illnesses and to assess response to anticytokine therapy.

IL-6 is a pleiotropic proinflammatory multifunctional cytokine produced by a variety of cell types, including lymphocytes, monocytes and fibroblasts. It has been shown to be involved in such diverse processes as T-cell activation, initiation of acute-phase proteins and stimulation of hematopoietic precursor cell growth and differentiation. IL-6 is also produced by synovial and endothelial cells, leading to local production in joints affected by inflammatory

processes, such as rheumatoid arthritis. Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody of the immunoglobulin IgG1 subclass, produced by recombinant DNA technology, that inhibits the function of IL-6. Total experience with tocilizumab for all indications extends to a total of more than 4800 patients as of June 2007. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit sIL-6R- and mIL-6R-mediated signaling. Clinical studies with tocilizumab have been performed or are ongoing in diseases such as adult-onset rheumatoid arthritis, sJIA and others (i.e., multiple myeloma, Castleman's disease, SLE and Crohn's disease).

Another example of advance from the bench to the bedside has emerged from the discovery and characterization of novel T-cell costimulatory pathways, in addition to the increasing understanding of conventional pathways. Inhibition of the CD28 costimulatory pathway has emerged as a rational therapeutic strategy for selectively modulating T-cell activation, and innovative technology in protein engineering has enabled the creation of CTLA-4Ig, which has been also used in a controlled trial for JIA.

Treatment with biologics has not only revolutionized the outcome of our patients, but has given new insights into the pathogenesis of inflammatory and autoimmune disorders. For example, the IL-1 receptor antagonist anakinra is highly efficacious in patients with auto-inflammatory diseases and in those with sJIA. However, within the latter group there seems to be a dichotomous mode of response, in that those patients who respond do so quite rapidly and impressively, while others seem not to have such a response. Therefore, it seems that patients can be classified according to their susceptibility to responding to certain biologics. It may well be that there are some patients whose disease is driven by a particular cytokine, but the simple dosing of the corresponding circulating substance is unlikely to give us precise answers regarding pathogenesis. Indeed, some conditions are associated with elevated serum levels of cytokines simply because they are readily secreted, but the cytokine does not necessarily have a pathogenic role. Therefore, response to treatment with anticytokines might also be helpful in elucidating the disease pathogenesis; a clinical lesson in cytokine-mediated diseases is that their causation can be established more

with specific receptor blockade or cytokine neutralization than with elevated circulating levels of the corresponding cytokines [31].

Treatment of systemic lupus erythematosus

Our understanding of the multiple physiological and pathological functions of B cells continues to expand at a fascinating rate, and these cells are known to play a major role in the pathogenesis of SLE by means of multiple mechanisms. The availability of effective agents capable of inducing B-cell depletion and the safety and efficacy of anti-CD20 (rituximab) in lymphoma has prompted investigators to use this therapeutic approach in a large number of autoimmune diseases. Thus far, results have been promising and more agents will be available in the future.

Supportive treatments

In addition to traditional treatments for rheumatic diseases, supportive measures are becoming increasingly important since the long-term outcome of these disorders is improving steadily. Among these, prevention of osteopenia and osteoporosis during the critical developmental stages of skeletal maturation is fundamental. New bone-specific treatments are now available, although their use for pediatric patients has been limited. Of all the new agents in clinical use, bisphosphonates (BPs) seem to be the most promising. BPs are analogues of pyrophosphate, and several chemical features contribute to their biological action: the P–C–P moiety gives these compounds the ability to adsorb to hydroxyapatite and target bone, while variations in the side chains determine the potency and spectrum of action of each compound. BPs are selectively concentrated in bone, and inhibit bone resorption by interfering with the action of osteoclasts. BPs have been extensively used in adults; until recently their use in pediatric patients has been limited by fear of adverse effects on a growing skeleton, because of the potential risks to a fetus if administered to a girl approaching childbearing age, and because the drug is not appreciably eliminated in the short to medium term. More recently, BPs have been shown to be quite safe, at least in the short term, even in pediatric patients, and their use has been expanding [32–37]. Adverse effects in children have not been reported in greater frequency than in adults. Osteomalacia does not seem to be a problem with the newer, nitrogen-containing BPs, although it has been reported in adults treated with etidronate. Hypocalcemia and fever are infrequent and

transient, and mild abdominal discomfort or dyspepsia are also occasional complaints. Radiological alterations described in prepubertal patients include band-like metaphyseal sclerosis and concentric epi- and apo-physeal sclerosis. However, no adverse effects on growth have been noted, even after a long follow-up, and the radiographic abnormalities tend to disappear after drug discontinuation. In two studies, we have shown that alendronate significantly improves bone mass in children or adolescents with rheumatic diseases and secondary osteoporosis [37,38]. However, many questions still remain unanswered. Will the positive effects last over time? For how long can this treatment be given? Will bone be more resistant to fracture? Are there any potential risks for young women in their childbearing years with respect to fetal toxicity? Will there be any unexpected medium- to long-term adverse effects? Will newer BPs be safer and/or more effective? At present, BPs should be considered as valuable tools, even in pediatric patients, but only for treating severe osteoporotic disease or in the setting of experimental protocols.

Growth delay also frequently accompanies chronic rheumatic disorders, with corticosteroids and inflammation playing a major role. Two recent randomized studies demonstrated good effects of recombinant human growth hormone initiated early in the course of JIA. Although recombinant human growth hormone was well tolerated, carbohydrate metabolism should be monitored closely [38,39].

For SLE, an additional problem is presented by premature atherosclerosis. SLE is an independent risk factor for atherosclerosis, placing children and adolescents with SLE at great risk for developing cardiovascular sequelae, including myocardial infarction, in adulthood. Routine screening for dyslipidemia with fasting lipid profiles is indicated for children and adolescents with SLE. If lipoprotein levels are abnormal, first-line therapy involves diet and exercise interventions for a minimum of 6 months. For persistent dyslipidemia, pharmacologic therapies are available. Hydroxychloroquine, a common treatment for SLE, can improve lipid profiles and should be considered for all patients with SLE. Statins and bile acid sequestrants are typically added first for dyslipidemia, while niacin and fibrates are reserved for refractory disease and optimally prescribed in a multidisciplinary lipid clinic. Statins may have added benefit in the management of pediatric SLE given their increasingly

recognized anti-inflammatory properties. There is an ongoing randomized, placebo-controlled study (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) investigating the efficacy of atorvastatin in preventing progression of carotid intimal-medial thickening, which will provide invaluable information concerning the use of statins in children and adolescents with SLE. Enrollment for this trial of 221 children and adolescents with SLE is complete and results are expected in 2010.

Kawasaki disease

This disorder holds a special place, since it is unique to childhood and represents the most common cause of acquired heart disease in the Western world. Many questions regarding diagnostic modalities, treatment and long-term outcome still are unanswered.

Diagnosis

Although 2D echocardiography still remains the gold standard in the early cardiac assessment of Kawasaki disease (KD) children and in detecting coronary artery aneurysms, new methods are needed in order to better visualize in detail the entire coronary artery system and the other cardiac structures, as well as their function [40,41]. To define the degree of cardiac damage, assessment of ventricular ischemia and myocardial blood flow is recommended. Dobutamine stress echocardiography has been shown to be a safe and sensible tool in evaluating the outcome of coronary artery anomalies (CAA), comparable to cardiac catheterization. Coronary magnetic resonance angiography has proved to be equivalent to x-ray coronary angiography, and is successful in the identification of coronary artery aneurysms and in their follow-up. Electron-beam computed tomography is a noninvasive tool that enables the early detection of myocardial ischemia progressing from the endocardial to central and epicardial regions, thus allowing a prompt therapeutic approach. PET has been reported to be useful in revealing flow reserve in children with normal epicardial coronary arteries, addressing the risk of residual coronary damage in the absence of evident coronary involvement. Recently, multislice spiral computed tomography has proved to be a non-invasive, sensitive tool comparable to coronary angiography in visualizing coronary artery stenosis; in the future, it could become the standard diagnostic tool and possibly replace angiography in patients with CAA.

Treatment

The recommended regimen in any patient with KD includes intravenous immunoglobulin (IVIG) (2 g/kg) as a single infusion over 8–12 h and aspirin (50–100 mg/kg in four divided doses); the prevalence of coronary artery abnormalities is dependent on IVIG dose but independent of aspirin dose. Possible mechanisms of action of IVIG include the effect of specific antibodies to infectious agents or toxins, anti-idiotypic antibodies, or nonspecific effects such as blockage of Fc receptors and accelerated clearance of complement fragments. No specific guidelines are available for the management of patients who are refractory to this treatment (10–20%). While a second infusion of IVIG is strongly recommended in all children with persistent or recurrent fever, no consistent proposals have been made regarding how to treat the small group still remaining febrile. Since previous studies reported high rates of coronary alterations in patients treated with corticosteroids, there has been some reluctance to use this therapy either as first-line treatment or as additional therapy in children who do not respond to IVIG. However, no association between corticosteroids and an increased incidence of CAA has been observed in more recent reports, and the use of corticosteroids (oral or intravenous) in children refractory to IVIG has been suggested as an alternative and safe treatment [42–47]. Other therapies that have been tried in cases of aggressive disease recalcitrant to IVIG and corticosteroids, mainly published as single case reports or small series, include cyclophosphamide, cyclosporine, ulinastatin and plasma exchange.

Serum levels of TNF- α are elevated in acute KD patients, with higher levels in those who develop coronary aneurysms. Infliximab, a monoclonal antibody against TNF- α , has also been successfully given to IVIG- and corticosteroid-refractory children with severe coronary involvement, and although results have been conflicting this represents a possible area of clinical research [48–50]. In fact, a randomized, prospective, clinical trial of infliximab 5 mg/kg versus repeat IVIG infusion for refractory KD is currently in progress at six clinical centers in the USA. The future of therapy for children with KD will include predictive testing based on both clinical parameters and genotyping in order to identify patients likely to fail initial IVIG therapy and/or those at highest risk for developing coronary artery aneurysms. Once identified, these patients will be candidates for more aggressive treatments, including anticytokines.

As long as the cause of this disease remains elusive, we will have at most only the possibility of nonspecifically suppressing the systemic inflammation. We are therefore anxiously awaiting results of experimental studies that are trying to elucidate its etiopathogenesis.

Prognosis

Many questions also remain unanswered [51–57]. Coronary arterial lesions are known to develop progressive intimal hyperplasia even many years after acute KD, and it may well be that even coronary arteries that appear normal on ultrasound may be damaged. Furthermore, KD may predispose to premature atherosclerosis in adulthood, and adverse cardiovascular risk profiles (low high-density lipoprotein and apo-A1 but high apo-B1 levels, and increased peripheral arterial stiffness) after resolution of acute inflammation have been detected in KD children with CAA when compared with those without CAA, and controls.

Conclusion

International collaborations in pediatric rheumatology were initiated many years ago, but it is only in the last decade or so that they have intensified and that initiatives have multiplied. Specialist centers should educate general pediatricians for a better screening of potentially harmful conditions, and keep the role of handling the more complicated cases. One major advance has been the Pediatric Rheumatology Bulletin Board, which has been very successful in gathering physicians from around the world with the common interest of dealing with pediatric rheumatic diseases. The only need is an internet connection, and difficult cases are discussed daily. Moreover, international organizations have expanded and the Pediatric Rheumatology European Society now has very successful annual meetings with over 400 participants from all over the world. The Pediatric Rheumatology International Trials Organization and Pediatric Rheumatology Collaborative Study Group have been instrumental in improving our quality of care, by running first-class clinical trials, and the Childhood Arthritis and Rheumatology Research Alliance has been fostering clinical research that will enable us to take better care of our patients. Finally, the *Pediatric Rheumatology Online Journal* (now *Pediatric Rheumatology*) has been the effort of an initially small group of individuals, led by Charles Spencer (Ohio State University, OH, USA), but is now indexed in Medline, and has free full-text access without the need for a subscription. All these initiatives are

likely to continue and expand, therefore providing the background for educating our young colleagues and for inciting many more to become interested in our fascinating subspecialty.

Future perspective

In the near future it is hoped that classification and diagnostic issues will evolve, based on new knowledge of diseases' etiopathogenesis. New definitions for flares and remissions in diseases such as JIA and SLE should be viewed as targets for interventional trials. The treatment armamentarium is also likely to increase, with more specific drugs engineered against biologic targets.

Overall, the prognosis of chronic rheumatic disorders of childhood is therefore likely to continue to increase steadily.

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Executive summary

Classification

- Diagnostic issues in pediatric rheumatic diseases remain a challenge despite the recent progress in molecular biology that has enabled the confirmation of some clinical descriptions proposed in the past. Any progress in classification of pediatric rheumatic diseases relies on excellent clinical observations, which can then allow targeted research.

Research

- Regulatory T cells have been found to be implicated in the pathogenesis of juvenile idiopathic arthritis.
- Novel antigen-specific treatments might be foreseeable as the exact role of these cells and their specificities will be elucidated.

Treatment

- The new biologics etanercept, infliximab, adalimumab, abatacept and rituximab have revolutionized the therapy and prognosis of our patients. More medications, including tocilizumab, rilonacept and others, are on their way.
- Treatment of disease complications, now that the long-term outcome has greatly improved, has gained more interest, and bisphosphonates have been increasingly used for secondary bone loss.
- The role of statins remains to be determined.

Special emphasis on Kawasaki disease & autoinflammatory disorders

- Kawasaki disease is still a dilemma for pediatric rheumatologists, since diagnosis remains clinical. New diagnostic modalities have been found to be useful in the evaluation of cardiac involvement. Patients with refractory forms will be likely to benefit from corticosteroids and TNF inhibitors. The long-term outcome of patients, both with and without coronary lesions, is still unknown.
- With regards to autoinflammatory diseases, clinical diagnosis in patients with unexplained recurrent or prolonged fever is now much easier owing to good clinical description backed up by genetic identification. Conversely, the knowledge of mutations allows the identification of atypical clinical aspects. Diseases associated with mutations in the *CIAS1* gene (encoding cryopyrin) form a group of disorders with overlapping characteristics.

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