Juvenile Idiopathic Arthritis: Towards Improving Clinical Care

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General introduction

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is the collective name of diseases characterized by chronic arthritis commencing in the pediatric age. The first descriptions of the disease dates back to as far as 1864-1900[1]. Initial organized attempts to classify the disease gave rise to the 1973 juvenile rheumatoid arthritis (JRA) criteria[2], hampered by difficulty of establishing criteria for a condition including more than one entity. In the years to follow important landmark meetings were held both in Europe and the United States: a new pediatric specialty was born. A new classification of Juvenile Chronic arthritis (JCA) by the European League against Rheumatism[3] was adopted in 1978. The two sets of criteria differed, hindering to compare research data overseas. A new consensus classification was introduced[4] which is currently still in use(see table 1). The umbrella term JIA is defined as any arthritis of unknown etiology with onset before the age of 16 years old and lasts for at least 6 weeks. Each category is mutually exclusive. In recent years systemic JIA has been recognized as an auto-inflammatory disease. This thesis focusses on patients with oligo-arthritis, polyarthritis and JIA with psoriasis.

The treatment of JIA consists of medical interventions and supportive care. In this thesis we focus on the medical treatment, supportive care is addressed in chapter 2.

Table 1 | International League of Associations for Rheumatology classification criteria for juvenile idiopathic arthritis in childhood

ILAR category	Characteristics	% of total
Systemic JIA	Arthritis and daily fevers ≥3 days, accompanied by at least one of the following: evanescent erythematous rash, generalised lymph node enlargement, hepato-/splenomegaly, serositis.	4-17
Oligoarticular Persistent Extended	Arthritis in 1-4 joints during the first 6 months of disease Arthritis in 1-4 joints through the entire disease course Arthritis in 5 of more joints after 6 months of disease	27-60 40 20
Polyarticular JIA RF+	Arthritis in 5 or more joints in the first 6 months of disease, at least two positive tests for rheumatoid factor at least 3 months apart.	2-7
Polyarticulair JIA RF-	Arthritis in 5 or more joints in the first 6 months of disease, negative tests for rheumatoid factor.	11-30
Psoriatic JIA	Arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nailpitting or onycholysis, psoriasis in a first degree relative.	2-11
Enthesitis related Arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: sacroiliac joint tenderness or inflammatory lumbosacral pain, HLA B27 antigen positive, onset in a boy> 8 years old, HLA B27 associated disease* in a first degree relative.	1-11
Undifferentiated JIA	Arthritis that does not fulfil criteria of one of the categories or meets criteria of more than 1 category.	11-21

*Ankylosing spondylitis, enthesitis related arthritis, sacro-iliitis with inflammatory bowel disease, Reiter's syndrome, or acute uveitis.

Antirheumatic drugs

Several drugs have been introduced for the medical treatment of patients with juvenile idiopathic arthritis. An overview of the most commonly used antirheumatic drugs is given here.

Medical treatment

Medical treatment for juvenile idiopathic arthritis was historically aiming at symptom relief and consisted after aspirin of non-steroidal anti-inflammatory drugs (NSAIDs) which became available in the seventees[5]. The first slow-acting antirheumatic drugs like penicillamine and hydroxycholoroquine appeared in the eighties for use in children and proved not to be effective in JIA.[6] Methotrexate (MTX) and to a lesser extent sulphasalazine (SSZ), were more successful and were registered for JIA in early nineties.[7,8] Methotrexate is still considered corner stone treatment for several categories of JIA[9].

Glucocorticoids are a therapeutic option for patients with non-systemic JIA in case of severe disease, as bridging therapy, while waiting for the response of systemic therapy, although evidence on its effectiveness is lacking[9]. Intra-articular steroids in the form of triamcinolonehexacetonide are effective and safe for the treatment of arthritis in children[28,29]. Recently it was suggested in retrospective studies that multiple injections were able to induce remission in a proportion of patients[30,31].

Sulfasalazine is one of the first antirheumatic drugs especially designed for the treatment of rheumatoid arthritis (RA) after its proven effectiveness for inflammatory bowel disease. It is a well-established DMARD for patients with RA either as monotherapy or in combination[10]. Its effectiveness in oligo- and polyarticular JIA was amongst others demonstrated in a multicenter randomized placebo-controlled trial in the Netherlands in 1992-1999[11]. A longterm follow-up study showed that the beneficial effects persist for many years[8].

Methotrexate (MTX) is an effective disease-modifying anti rheumatic drug in children with JIA. At a dose of 10 mg/m^2/week MTX has been shown to have a significant therapeutic advantage over placebo and an acceptable safety profile[7]. A plateau of efficacy is reached with parental administration of 15 mg/ m^2/week[12]. The response to MTX may be inadequate in some patients, even at higher dosages, and lack of tolerability limits its usefulness sometimes[13,14]. Due to suspected increased bioavailability a subcutaneous dosing regime is advised at higher dosages[15,16]. An initial robust response to MTX is predictive for a better long term outcome[17]. Remission rates vary greatly from 7-45%[18-20]. Relapse rates before the year 2000 were quite high, over 50% although reported in small series[21,22]. Foell et al studied the optimal moment to stop MTX in JIA patients in a retrospective analysis and did not see a difference in terms of flare frequency in case of longer MTX therapy (mean

3.8 vs mean 12.6 months)[23]. This result was confirmed in a multicenter, 12 vs 6 months withdrawal MTX study. In both groups flare rate was almost 40% within 1 year despite longer treatment with MTX in the 12months group[24].

Hydroxychloroquine, an antimalarial, is known since the 1950s in the treatment of rheumatoid arthritis. It was first applied in a study in JIA patients in the eighties and proved ineffective[6]. It is one of the least potent antirheumatic drugs, but still in use as an adjunct to combination therapy in rheumatoid arthritis[25]. Although the role of hydroxychloroquine as adjunct therapy has been subject of study[26], convincing evidence is still lacking and this remains subject of further study.

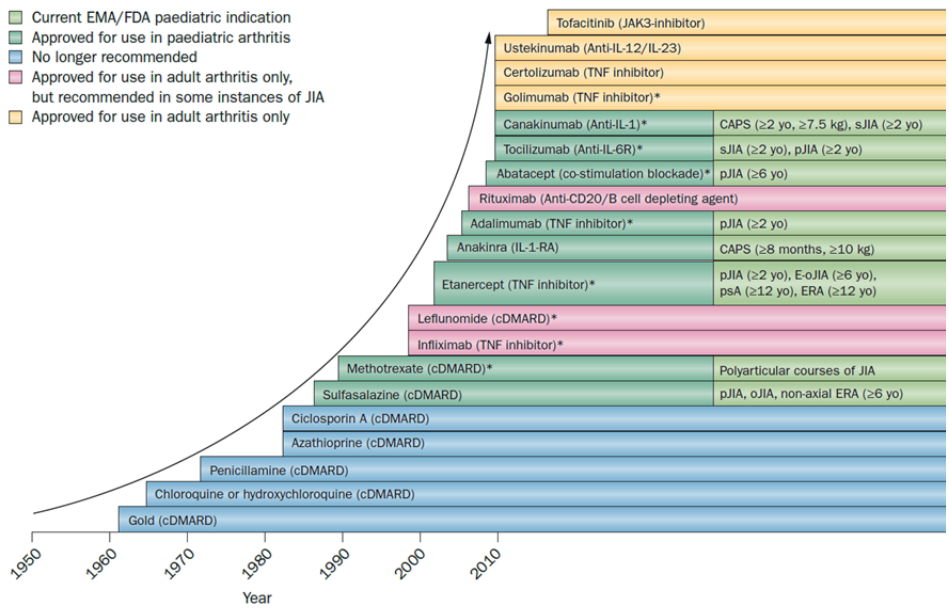

Figure 1 | The armamentarium of antirheumatic drugs available for the treatment of JIA. The evolution of biologic DMARDs in past decades revolutionized the therapeutic management of arthritis. However, although the number of variety of therapies available for use in paediatric rheumatology (excluding glucocorticoids and NSAIDs) is greater than ever, deciding on a treatment strategy has correspondingly increased in complexity. Whereas some therapies have been tested in high-quality paediatric studies, only some have received specific approval for use in children with rheumatology diseases, and such approval may also be limited to certain JIA categories. Additionally, soms drugs approved in adult rheumatology have been recommended for use in JIA without EMA or FDA approval. *Therapies tested in high-quality paediatric studies. Abbreviations: CAPS, cryopyrin-associated autoinflammatory syndromes; cDMARD, conventional disease-modifying drug; EMA, European Medicines Agency; E-oJIA, extended oligoarticular juvenile idiopathic, arthritis; ERA, enthesitis-related arthritis; IL-1-RA, IL-1 receptor antagonist; JIA, juvenile idiopathic arthritis: oJIA, oligoarticular juvenile idiopathic arthritis; pJIA, polyarticular juvenile idiopathic arthritis; psA, psoriatic arthritis; sJIA, systemic juvenile idiopathic arthritis; TNFi, tumour necrosis factor inhibitor; yo, years old.

Figure from: Management of juvenile idiopathic arthritis: hitting the target
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Leflunomide, a reversible inhibitor of de novo pyrimidine synthesis, was studied in polyarticular JIA only in one open-label trial[27]. ACR30 response criteria were met in the majority in the short and long term.
By the end of the last century a new category of medication appeared with the development of the biologicals.

Bioogic treatment in JIA: what do we know up to now?
Technical developments and better understanding of the disease process led to the development of monoclonal antibodies against an important cytokine in juvenile idiopathic arthritis, tumor necrosis factor-alpha, TNF-α.
Since the development of biologicals and the first use in juvenile idiopathic arthritis almost 2 decades have past. Initially the effectiveness of etanercept was established in severe treatment refractory JIA[32 33].
Dedicated observational studies have taught us about the effectiveness and improved quality of life in JIA patients treated with anti-TNF[34-36]. The safety profile, both in the short and long term is good[37-40]. Prolonged use up to 5 or even 10 years is described[34,38,41,42], underscoring its effectiveness and tolerability. Growth in JIA patients seems to be restored in treatment with etanercept[43-45]. The efficacy does not change when etanercept is given in a once weekly dose[46].

Secondly adalimumab[47], infliximab[48] and biologicals with other modes of action were studied[49-51] and often subsequently approved in JIA treatment.
As the years are passing, biologicals are used more often and earlier in the disease course[52]. Their place in the treatment of patients with recently diagnosed JIA and their effectiveness compared to other aggressive treatment strategies has yet to be determined[53,54].

Bottom up or top down?
Although the medical treatment in JIA depends to a large extent on the category of JIA, improved disease outcome has been achieved by early and aggressive immunosuppressive treatment, instead of by a gradual add-on approach of medication in case of ongoing disease activity[55]. The ultimate outcome is irrespective of the JIA category: destruction of joints resulting in severe incapacity can occur in children with oligoarticular JIA, while some children with severe polyarthritis at onset can easily reach inactive disease within weeks when responding to medication[55,56]. Despite advances in treatment options and modalities during the last decade, a considerable number of children with JIA remain refractory to therapy[57]. The overall outcome of JIA needs to be improved while children are still developing joint damage and/or limitations in daily functioning[58]. Many patients with JIA continued to have active disease 10 years after onset, with persistence of active

disease into adulthood as well[8,59]. In a longitudinal study by Wallace et al. evaluating 437 patients with JIA over a median follow-up of 7 years showed that during the entire course of the disease, the patients spent less than 35% of the time in a state of clinical remission off medication, regardless of the JIA subcategory[60]. Ringold described in 2009 a cohort of patients who spent the majority of their follow up time in active disease[61]. These data highlight the urgent need for improved treatments in JIA that are capable of inducing extended periods of clinical remission off medication. It is unclear how to position the available drugs in JIA in daily practice. The traditional (bottom up) approach was to 'go low, go slow', aiming to avoid in part unknown side effects of the available drugs. This approach to drug treatment emphasizes the stepped use of one disease modifying antirheumatic drug (DMARD) at a time. When first-line agents such as nonsteroidal anti-inflammatory drugs (NSAID) failed after months "second-line", "slow-acting" or "DMARDs" such as antimalarial agents, sulfasalazine (SSZ), methotrexate (MTX) were considered. In the past years a shift to an earlier introduction and more aggressive combination (top down) therapy was seen although comparative trials of different combinations lacked in JIA at the start of this thesis. A too cautious approach can lead to undertreatment and permanent disability.

The current approach in 2009 to the treatment of children with oligoarticular JIA was to start with a NSAID and/or intra-articular glucocorticoids. When that is not effective, to add SSZ and/or MTX, Patients with extended oligoarticular JIA, Rf negative polyarticular JIA and psoriatic arthritis also usually start with a NSAID. When that is not effective SSZ and/or MTX are added. MTX first in a relatively low dose, next a higher dose, sometimes with prednisone bridging. Only for patients with polyarthritis who have shown to be MTX resistant or for those who do not tolerate MTX the TNF-blocking agents are available. Studies have shown this to be a very effective drug, both on clinical outcome measures and on radiological damage progression[37,62]. In 2011 ACR recommendations were published to guide treatment for JIA[9], discerning three levels of disease activity, low, moderate and high, by recognizing features of poor prognosis, like radiographic damage at presentation or involvement of hip or cervical spine.

Combination therapy

At the start of this thesis (2009) combination therapies were not commonly administered to JIA patients. In several trials, patients already treated with MTX receiving new biological therapies were treated with MTX as co-medication in varying percentages of patients[50,63,64]. After the success of combination therapies in rheumatoid arthritis, studies on initial combination therapies were first described in 2011 and onwards, although in the recommendations by Beukelman[9] no advice is formulated on non-biological DMARD combinations due to a lack of evidence.

The TREAT study, a randomized blinded placebo controlled trial and the ACUTE JIA trial, with a randomized open-label design, both used the combination of methotrexate and antiTNF: (etanercept in TREAT, infliximab in ACUTE). Both trials demonstrated that early use of a biological agent resulted in higher frequencies of inactive disease.

Window of opportunity

As shown in the BeSt study in rheumatoid arthritis patients[65,66] it is likely that also in JIA a window of opportunity exists where the disease is most responsive to treatment and susceptible for permanent suppression. In several papers the existence of this window of opportunity in children with JIA was illustrated[8,67]. When inactive disease can be achieved during an early phase, the opportunity arises to discontinue the treatment, thus shortening the time of exposure to possible side effects of drugs.

Discontinuation of anti-rheumatic drugs

What is known from literature about stopping treatments in JIA? As mentioned previously stopping methotrexate is feasible with the risk of flare approximately 40% irrespective of treatment continuation for 6 or 12 months[24]. Tapering or stopping TNF inhibitors has been evaluated in several retrospective studies[68-73] which were all published after the onset of the study serving as the basis of this thesis. Flare rates are overall high varying from 50-69%. In the large recent prospective cohort study from Guzman et al[74], flares occurred in over 50% of patients, although significant flares requiring additional treatment occurred within the first year after stopping therapy in 25%.

Monitoring of clinical response

By the end of the nineties the ACR Pedi improvement scores were published[75] to aid in standardization of the conduct and reporting of clinical trials and additionally to facilitate the physician to determine whether a patient responds adequately to therapy.
The JIA Core Outcome Variables consist of:

1. Physician Global Assessment of Disease Activity (10 cm Visual Analogue Scale (VAS))
2. Parent/patient global assessment of overall well-being (10 cm VAS)
3. Functional Ability (Childhood Health Assessment Questionnaire)
4. Number of Joints with Active Arthritis
5. Number of Joints with Limitation of Movement
6. Erythrocyte Sedimentation Rate ESR.

For efficacy assessment, patients will be evaluated as “improved” or “not improved” by comparing the values of core outcome variables at the post-dose assessment time points with baseline values.

Definition of Improvement in Juvenile Idiopathic Arthritis

JIA ACRPedi30/50/70/90 improvement is defined as 3 of any 6 core outcome variables improved by at least 30/50/70/90% from the baseline assessments, with no more than 1 of the remaining variables worsened by more than 30%.

The advantage of reporting outcome measures uniformly proofed beneficial in comparing clinical data. However the relative improvements does not reflect actual disease status and prevents comparison of disease activity between patients. Additionally it is not easy to use in daily practice.

JADAS score

Therefore more recently the Juvenile arthritis disease activity score (JADAS-71,-27, or-10) was developed and validated[76].

The scores of 4 domains are added:

1. Physician Global Assessment of Disease Activity (0-10 cm Visual Analogue Scale (VAS))
2. Parent/patient global assessment of overall well-being (0-10 cm VAS)
3. Number of Joints with Active Arthritis (0-10 count of any involved joint, irrespective of its type, up to a maximum of 10 joints.
4. Normalized ESR; (ESR-20)/10; all values ESR above 120 are converted to 120, all values <20 are converted to 0.

To a maximum of 0-40 (JADAS-10) 0-57 (JADAS-27) and 0-101 (JADAS-71).

Since then adjustments were developed to a 3-point score, which facilitates use in a daily clinic because it is not necessary to wait for the sedimentation rate to determine the disease activity score[77]. Cut-off values for various disease states are available for use in clinical trials[78,79].

Definition of inactive disease in Juvenile Idiopathic arthritis

Wallace defined inactive disease in 2004[80] which was adopted in the study design of the BeSt for Kids study: Inactive disease is characterized by criteria: no clinical symptoms of active synovitis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR and/or CRP; Physician´s global assessment of disease activity indicates no active disease. In addition to this definition the duration of morning stiffness of ≤15 minutes was added as criterion for inactive disease in 2011.[81]

Child Health Assessment Questionnaire

The Child Health Assessment Questionnaire is a measure of functional status, which is disease specific for JIA[82,83]. Both disability and discomfort are tested focused on physical functioning. Eight domains are tested including dressing, grooming, eating and different general physical abilities divided over 30 items questioning difficulty in performance. The CHAQ score is calculated as the mean of the 8 functional areas. The final score is 0-3. Values of 0.13, 0.63, and 1.75 have previously been described to represent respectively mild, mild to moderate, and moderate disability[84]. A change in score of 0.13 represents an important change in clinical status[84,85]. The test is easy to use and short, therefore increasingly used in clinical trials as well as longitudinal studies. The test is characterized by good reliability and validity, as well as good discriminative properties and reasonable responsiveness[86].

Monitoring of radiographic damage

Over the years several scoring systems for assessing joint damage and progression have been developed[87]. Since in children growing joints change anatomically over time, it is not easy to determine cartilage loss and erosions. This unique feature of growth in children limits the use of the most well-known scoring system from adult rheumatology: the Sharp-van der Heijde score in its original form[88]. A pediatric adaptation (adding 5 areas in the wrist and omitting to score the feet, since foot joints are rarely involved in JIA) to the Sharp-van der Heide score was developed and validated[89] and has been used, although few, eversince[90,91]. The older and more easy to perform Poznanski score[92] is a measure of the ratio between carpo: metacarpal length and reflects the amount of radiographic damage in the wrist. Poznanski scores that are more negative represent more severe radiographic damage[62,93-96].

Which target are we aiming at?

Classically the ACRpedi30% was regarded as the clinical target in studies[75], reflecting 30% improvement in at least 3 out of 6 core set variables, with no more than one of the remaining variables worsening by more than 30%. As such this target was used in several trials.[32,97,98] Against the background of all improvements due to increasing therapeutic options, mainly the introduction of etanercept, this target was gradually regarded as too low. In trials as well as observational studies ACRpedi50 and 70% became alternative targets[26,38]. In clinical care inactive disease was gradually recognized and mentioned as the target to aim at[99]. It took some time however before inactive disease was chosen as the primary outcome measure in a JIA clinical trial, as was proven to be a realistic target in RA[65].

The BeSt for Kids study

Despite new therapeutic options, it is still unclear how and when a drug or combination of drugs should be introduced over time in patients with juvenile idiopathic arthritis. Previous studies focused on the comparison of one drug or the combination with another drug or combination. More relevant for clinical practice is what consecutive therapeutic steps should be taken when disease activity is insufficiently suppressed. Additionally with inactive disease as a therapeutic target, which strategy results in the best long term outcomes, with the least side effects? Should all patients be treated initially with a combination of antihreumatic drugs or biologic agents, or can they be reserved for patients who fail on initial monotherapy? There are concerns about the long-term safety of more aggressive approaches, especially about infections and malignancies although results up to today are reassuring. Financial restrictions preclude treatment of newly diagnose JIA patients with expensive TNF-antagonists in many countries.

Against this background, and after the success of the BeSt study in RA[65], the BeSt for Kids study was developed by a group of (pediatric) rheumatologists. In this study three treatment strategies are compared (figure 1 page 99).

1 Sequential monotherapy, starting with methotrexate or Sulphasalazine, thereafter increasing MTX dose or switching to MTX, thereafter adding etanercept (anti-TNF).
2 Initial combination therapy with methotrexate and prednisolone bridging therapy, thereafter increasing MTX dose, thereafter adding etanercept (anti-TNF).
3 Initial combination therapy with methotrexate and etanercept (anti-TNF).

For patients failing on their medication, the treatment protocol prescribed a number of subsequent treatment steps. The decision whether or not to adjust medication was made every three months based on ACRPedi50% after initial 3 months, and based on inactive disease from 6 months and onwards. To avoid bias, the joint examination was performed by a physiotherapist or research nurse who remained blinded for the allocated treatment group during the entire study period. If the target (ACRpedi50% or inactive disease) was not met, the treating physician immediately adjusted therapy by proceeding to the next step in the allocated treatment group. In the target was met for at least 3 (oligoarticular disease) or 6 (polyarticular disease) months, medication was tapered and stopped according to a predetermined protocol. To avoid overtreatment of patients with oligoarticular JIA especially in the arm with initially etanercept and methotrexate the required duration of inactive disease is chosen to be three months for those patients. This study combined three study questions in one study: 1 Can we achieve inactive disease, 2 can we taper and stop DMARD therapy and if we can, 3 what is the flare frequency?

JIA categories under study

Three categories of JIA will be studied: oligoarticular JIA (both with persistent and extended phenotype), RF-negative polyarticular JIA and juvenile psoriatic arthritis. Inclusion of children with extended oligoarticular JIA, RF-negative polyarticular JIA and juvenile psoriatic arthritis when they need a DMARD probably warrants no further discussion. We have chosen to also include children with persistent oligoarticular JIA that continue to have active synovitis despite treatment with NSAID's and/or intra-articular glucocorticoids, considering the fact that in these patients outcome is highly variable. Albers et al[100] in a cohort of patients with JIA reveal that the percentage of time with active disease in the first two years after diagnosis is an objective parameter of the course of disease and is highly variable in all JIA categories. Within each category of JIA, patients can have a wide range of duration of disease activity varying from a short duration of time with active disease to ongoing disease activity.[100] The incidence of the other categories of JIA, for instance RF-positive polyarticular JIA, is too low to allow stratification.

Outline of this Thesis

This thesis consists of two parts. The first part describes three studies related to pathogenesis of JIA and the second part describes the results of a treatment strategy study in JIA, the BeSt for Kids study.

Part One Aspects of Pathogenesis of JIA

First the pathogenesis of JIA is reviewed against the latest research novelties in **chapter 2**. One of our objectives was to discover the role of the newly recognized antibodies in rheumatoid arthritis, the anticarbamylated proteins. In **Chapter 3** anticarbamylated proteins were studied in a large cohort of JIA patients, combined from the ABC-register and the BeSt for kids cohort.

Novel in the pathogenesis of auto-immune diseases in general and JIA in particular is the possible role of the intestinal microbiome. One of the first (pilot)studies worldwide between the onset of JIA and the possible role of the composition of the microbiota was initiated in JIA patients generated from the BeSt for Kids cohort and will be described in **chapter 4**.

Part Two Treatment Strategies in JIA

The BeSt for Kids study serves as the basis for this thesis. In this single-blinded multicenter randomized 3-armed treatment strategy study sequential monotherapy with either Sulphasalazine or Methotrexate (arm 1) is compared to initial combination therapy with Methotrexate and prednisolone (arm 2), and with initial combination therapy with etanercept and MTX (arm 3). In **chapter 5.1** we describe the 3-months clinical results of the

three treatment strategies in early onset JIA. The long term (24 months) clinical outcome is set out in **chapter 5.2**. **Chapter 6** deals with the results of the radiological outcome of the BeSt for Kids study. An interview study was conducted to decipher aspects of clinical equipoise in the BeSt for Kids study, set out in **chapter 7**. As the study proceeded one patient was wrongly diagnosed and included in the BeSt for Kids study due to a JIA mimic. **Chapter 8** describes the disease course as the patient had to be excluded from the BeSt for Kids study, secondarily diagnosed as systemic polyarteritis nodosa (PAN). The general discussion is presented in **chapter 9** and the summary is given in **chapter 10.**

Notes

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