Juvenile Idiopathic Arthritis: Towards Improving Clinical Care

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Summary
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Summary

In this thesis, the central theme is the treatment of JIA, as well as some aspects of the pathogenesis.
In part 1 on pathogenesis, two pilot studies are discussed. The first study discusses the presence of anti-carP antibodies in sera of JIA patients and the second study is on the role of the microbiome in JIA.

The results of the BeSt for Kids study are documented in part two: the clinical section.

Chapter 2 describes, in a nutshell, the latest developments in pathofyiology and treatment of oligo and polyarticular JIA. The pathogenesis is determined by a combination of factors, the most important of which are: genetic predisposition, environmental factors, triggering infections and hormonal factors. An expanding amount of treatment options has become available in the last 20 years, of which the biologicals are the most important group.

Evidence for the existence of a window of opportunity is increasing, when the disease is most susceptible for (permanent) modification. The optimal treatment strategy has not been determined yet. The conclusion is that it is the biggest challenge of this time to treat the right JIA patient at the right time with the right medicine.

Chapter 3
In chapter 3 we describe a study that determines whether anti-CarP antibodies are present in sera from JIA patients. In patients with rheumatoid arthritis (RA), the presence of anti-CarP antibodies is associated with a poor prognosis, independent of anti-CCP / ACPA (antiCyclic citrullinated protein) or rheumatoid factor (RF). Sera from 234 JIA patients from 3 different cohorts were examined for the presence of anti-CarP antibodies. Anti-CarP antibodies were more frequently detected in sera from JIA patients (8-13%) than in sera from healthy controls (3-5%).
About half of the anti-CarP positive cases were also positive whether RF or ACPA was positive. Anti-CarP antibodies were also found in ACPA and RF-negative JIA patients. The prognostic value of anti-CarP in JIA has yet to be determined but has low prevalence.

Chapter 4
In the pilot study described in chapter 4, the composition of the gut microbiome in children with JIA was compared with healthy controls. With the so-called IS-Pro technique, molecular detection can take place on the basis of the 16S rDNA region, which is characteristic per microorganism. Based on a specific analysis called PLS-DA (Partial Least Squares Discriminant

Analysis), the gut microbiota profiles of 8 JIA patients could be distinguished from 22 healthy controls, based on differences in the phylum Bacteroidetes. Phylum Bacteroidetes plays an important role in the healthy microbiome. More studies are needed to unravel the role of the microbiome in the development of JIA.

PART II

Chapter 5

In chapter 5 the results of the BeSt for Kids study are reported, which form the basis of this thesis. In this single-blinded, randomized, multicenter treat-to-target (T2T) strategy study, 3 treatment strategies are compared in terms of effectiveness and safety in children with recent-onset JIA. The treatment arms are: 1) Starting with sequential therapy, one drug at the time, starting with sulfasalazine (SSZ) or methotrexate (MTX) (depending on the choice of the physician) 2) Initial combination treatment of methotrexate with 6 weeks prednisone and 3) in the beginning combination treatment of methotrexate with etanercept. This is the most innovative arm because etanercept up to present is only available for children with JIA who have failed on MTX or are intolerant to this. The first outcome measure is the time-to-inactive-disease after starting the treatment. A second outcome measure is the time-to-flare after tapering and stopping the anti-rheumatic medication. Improvement is measured according to adjusted ACR Pedi score 30, 50, 70 or 90% and inactive disease. Furthermore, we looked at safety and quality of life.

In **5.1** the results are discussed after the first 3 months of treatment.

Ninety-four children were included, including 32 in arm 1 and in arm 2 and 30 in arm 3, median age at inclusion of 9.1 (4.7-12.9) years. ANA positive was 38%, 12 patients had oligo articular disease, 68 polyarticular and 15 JIA with psoriasis (also polyarticular). Baseline median (IQR) ACRpedi scores: VAS doctor 49 (40-58) mm, VAS patient 54 (37-70) mm, BSE 6.5 (2-14.8) mm/hr, number of active joints 8 (5-12), number of limited joints 3 (1-5), CHAQ score 0.88 (0.63-1.5). In arm 1, 17/32 started with MTX. An intention-to-treat analysis was performed. Toxicity was similar. There were few serious side effects reported. All without permanent injury.

After 3 months of treatment, the following improvement was found:

	arm 1 Sequential monotherapy n=32	arm 2 Combo MTX+6 wks prednisone n=32	arm 3 Combo MTX+ etanercept n=30	p
aACRpedi30 (%)	16 (50)	17 (53)	22 (73)	0.13
aACRpedi50 (%)	10 (31)	12 (38)	16 (53)	0.19
aACRpedi70 (%)	8 (25)	6 (19)	14(47)	0.04

In conclusion, after 3 months of treatment in a 3-arm strategy study, more clinical improvement in the form of ACRpedi70% was achieved on the initial treatment combination of etanercept with MTX than on initial monotherapy with MTX or SSZ.

In **5.2** the long-term outcome after 24 months follow-up is summarized.

In this follow-up treat to target (T2T) study the central question is what the optimal treatment strategy is over the longer term. The initial treatment in 3 arms consisted of 1) Initially sequential DMARD monotherapy, starting with SSZ or MTX (depending on choice of physician) 2) Initial combination treatment of methotrexate with 6 weeks prednisone and 3) in the beginning combination treatment of etanercept and MTX . In the case of persistent disease activity, treatment was intensified according to protocol. In case of persistent inactive disease during 3 (oligoarticular disease) or 6 (polyarticular disease) months, the treatment was phased out and stopped. After 24 months, the first outcome measures were time-to-inactive-disease and time-to-flare after stopping medication. Secondary outcome measures were adjusted ACRpedi30/ 50/70/90 scores, functioning and toxicity.

Of the 94 children who were included, 2 were lost-to-follow-up and 2 others had a revised diagnosis. As a result, baseline characteristics were determined again. At start, these were the initial values: VAS doctor 50 (39-58) mm, VAS patient 54 (37-70) mm, BSE 6 (2-14) mm/hr, number of active joints 8 (5-12), number limited joints 2.5 (1-5), CHAQ score 0.9 (0.6-1.5).

Time-to-inactive disease was median 9 (6-12)months and was not significantly different between the arms. Time-to-flare was median 3.0 (3.0-6.8) months, not different between the 3 strategies. The adjusted ACRpedi scores were similar. After 24 months, 71% (arm1), 70 % (arm2) and 72% (arm3) achieved inactive disease. Up to 45% (arm 1) 31% (arm 2) and 41% (arm 3) of the patients had stopped using all DMARD (s). Toxicity was similar. In

conclusion, more than 70% had inactive disease in each arm and up to 39% had stopped all DMARDs. No statistically significant differences were found, suggesting that treatment-to-target, aimed at inactive disease, is feasible and more important than initial treatment strategy.

Summary of results

	arm 1 Sequential monotherapy n=31	arm 2 Combo MTX+6 wks prednisone n=32	arm 3 Combo MTX+ etanercept n=29
Time to ID(m))	9.0 (5.3-15.0)	9.0 (6.0-12.8)	9.0 (6.0-12.0)
Timing of first DFID, mnths	15.0 (12.0-18.0)	19.5 (12.0-24.0)	18 (12.0-21.0)
Drug free ID	19/31, 61%	16/32, 50%	19/29, 66%
ID after 1 year (%)	54	47	62
ID after 2 yr (%)	71	70	72
DFID after 2 yr (%)	45	31	41
Time to flare (mth)	4.5 (3.0-9.0)	3.0 (3.0-3.0)	3.0 (3.0-6.8)
Flares	6 (1=oligo)	3	5
JADAS-10 1 year	6.1 (3.8-8.3)	6.2 (3.8-8.6)	4.7 (2.6-6.8)
JADAS-10 2 year	2.6 (1.4-3.8)	4.0 (2.2-5.8)	3.0 (1.6-4.4)
JADAS ID 1 year	8.4 (27%)	9 (28%)	9 (31%)
JADAS ID 2 years	16.2 (52%)	14.1 (44%)	12.5 (43%)

In Chapter 6 is reported on the radiological outcomes of the children that participated in the BeSt for Kids study. The aim of the study was to evaluate the response to early aggressive treatment using conventional X-rays of the affected wrists. An additional goal was to compare 2 methods for evaluating the presence and progression of radiological damage in the wrist. The Poznanski-score, in which the relative carpal length is measured, was used as a measure of the radiological damage in the wrist. The bone age and bone density were determined with the help of BoneXpert, an automated program that is proven to be feasible and easy to use. X-rays of 60 children were available for evaluation. With regard to the Poznanski-scores, starting and follow-up scores did not differ from each other and not from a healthy population. Bone age was also comparable with start and follow-up measurement. Bone mineral density was significantly reduced at baseline in arm 3 compared with healthy controls and improved significantly in subsequent post-treatment studies. In conclusion, we found no radiological damage in the wrist in this cohort of children with JIA who were treated early and to target.

Chapter 7 discusses the concept of equipoise in patients and / or parents against the background of the BeSt for Kids study. Equipoise means sincere uncertainty with respect to the superiority of one treatment over the other. Physician researchers need equipoise to perform randomized controlled trials (RCTs), at least in studies with more than minimal risks. Whether this equipoise is also present in patients and parents in clinical trials is unclear. Participating children and their parents were asked about their preference immediately upon inclusion in the BeSt for Kids study with the aid of a questionnaire (phase 1). During an interview study (phase 2) to evaluate the equipoise in parents/patients who participated in this study preferences were questioned again. Semi-structured interviews were held with 23 parents and 7 patients older than 12 years, 11 months on average after inclusion in the study. Most parents and patients were initially not in equipoise. Many in phase 1 preferred arm 3, initial treatment with a biological. They participated in the study because of this opportunity and would even stop participating if they had not drawn arm 3. The conviction that the strategy with initial treatment with a biological (arm 3) was superior, was based on knowledge obtained via the internet and close relations. Four parents were convinced that the physician-researcher had a preference for arm 3, while the majority (n=19) felt that the physician-researcher had no preference. In phase 2, the preferences tended to change to the actual strategy in which the patient was randomized.
In conclusion, we argue that parents of children who participate in studies have preferences in treatments. It is important to understand all concerns and values of parents of children participating in studies. Their preferences may change over time, especially in an unblinded context. Moreover, their preferences may differ from the preferences of the physicians involved.

A study that does not correspond to the concerns of the relevant patient group is unlikely to be supported by this patient group. In future studies it pays to examine the equipoise of the 'informed patient group' as a whole, to improve recruitment of patients in studies.

In chapter 8 we discuss a special case history of one of the participants in the BeSt for Kids study. Following the diagnosis of juvenile idiopathic arthritis (JIA), she was treated with arm 3 after inclusion, initially etanercept and methotrexate. The primary diagnosis JIA was based on symmetric polyarthritis with no signs of systemic involvement. Six months later she developed myalgia, hypertension and fever with elevated inflammatory parameters. The combination of symptoms along with angiographic abnormalities in the kidneys led to the diagnosis of juvenile systemic polyarteritis nodosa (PAN). Juvenile PAN is a rare inflammatory disease in which small to medium-sized muscular arteries are affected. The highly variable clinical presentation is caused by the large amount of potentially involved organs. The diagnosis can be difficult because the first symptoms are non-specific and often

can mimic other inflammatory diseases. Although juvenile PAN is a rare disease, it belongs in every differential diagnosis of undetermined systemic complaints or inflammatory diseases.

Chapter 9 reflects on the results of this thesis against the background of current clinical care. Results of our studies are compared with previous studies. Secondly our and other studies are reviewed in terms of design and treatment target. Lessons to be learned from this thesis are:

- Treatment to target combined with tight control are feasible in a JIA clinical trial and give additional benefit in the short and long term treatment of juvenile idiopathic arthritis.
- Inactive disease should be the target to aim at after 6 months of treatment and onwards.
- Tapering strategies can be introduced in JIA studies safely since flare frequency was low and responses to restart of medication were good.
- Radiographic damage did not occur in any of the study arms and bone mineral density significantly increased after treatment to target in the third arm (initial etanercept and methotrexate).

Current research is focused on reaching inactive disease and reducing disease and therapy burden. Future research will focus on personalized therapies combined with treatment-to-target strategies aiming at inactive disease.