Mesenchymal stromal cells for treatment of drug resistant pediatric Juvenile idiopathic arthritis

Published: 18-09-2013
Last updated: 24-04-2024

To find out if intravenous MSC is a safe treatment for children with therapy-resistant JIA

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON39754

Source
ToetsingOnline

Brief title
MSC-JIA

Condition

- Autoimmune disorders
- Joint disorders

Synonym
juvenile idiopathic arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMw Translationeel Adult Stamcelonderzoek (TASO-grant)

Intervention

Keyword: drug resistant, juvenile idiopathic arthritis, mesenchymal stem cell, mesenchymal stromal cell

Outcome measures

Primary outcome

Total number of adverse events in the 3 months prior to MSC infusion and the

number of adverse events 3 months after MSC infusion.

Secondary outcome

The ACR Pediatric 30 criteria should be met.

The ACR Pedi 30 criteria are defined as improvement of >= 30% in at least 3 of 6

core response variables used to assess disease activity with no more than 1

variable worsening by >= 30%.

Clinical outcomes:

Clinical visits (at least 7 times in the first year 0-51 wks): -13, 0, 4, 8,

12, 16, 26, 39, 52 weeks

The visits will encompass complete medical history and monitoring for side

effects. Furthermore complete physical examination including total joint count.

Validated health and functionality related questionnaires (see below) will be

provided to the parents/patients. Global assessments by the parents/patients

measured with a 10-cm VAS.

Most widely used questionnaire for JIA is the Childhood Health Assessment

Questionnaire (C-HAQ 30+8).

In children with JIA, a functional measure focused to assess the function of

individual joint groups, the Juvenile Arthritis Functionality Scale (JAFS), detects with greater precision the functional impact of arthritis in specific body areas than does a standard questionnaire based on the assessment of activities of daily living (the C-HAQ).

Normal evaluation of JIA includes: articular index of tender joints, evaluation of the joint range of motion (EPM-ROM scale) 44 and will contain an evaluation of all joints as described previously. In short the joints will be assessed as being normal, warm, painful/tender, tender on passive motion, limited in motion. The degrees of passive motion will be noted for all limited joints.

Global assessments by the physician measured with a 10-cm visual analogue scale (VAS).

A weighted joint score improves the information provided by joint counts on the severity of arthritis and its impact on patients' well-being since a small finger joint of the non-dominant hand does not have the same impact as a knee that's is involved.

ACR Pedi 30, 50, 70 and 90-scores are most frequently used for clinical trials.

A composite disease activity score for JIA, the Juvenile Arthritis Disease Activity Score (JADAS), has the advantage of the measurement of actual disease activity and the comparison of one patient's absolute response with that of another patient's since it quantifies the absolute level of disease activity by providing one summary number on a continuous scale. All the above will be evaluated since all these parameters are complementary.

Lastly the proposed preliminary definition of minimal disease activity in polyarticular JIA, the proposed preliminary definition of inactive disease in

polyarticular JIA and the cut-off values for various disease states for the JADAS scores will be evaluated.

Radiological outcomes:

Magnetic Resonance Imaging (MRI 3x): MRI will be performed before MSC-infusion (wk0), 8 weeks (wk8) and 1 year after MSC infusion (wk52)

The most active (highest burden in pain/swelling/limitation) large peripheral joint will be imaged; if only small joints of hands or feet are involved a whole hand or foot will be imaged. No data on treatment will be provided to the radiologist.

Synovial enhancement, bone edema, cartilage loss, and bone erosion will all be scored as absent, mild, moderate and severe in both joints. Overall, there is fair (grade B) strength of evidence that MRI is an accurate diagnostic method for evaluating synovium and cartilage and for assessing clinical responsiveness to treatment in peripheral joints in JIA. In the case of knees the JAMRIS score can be used.

Laboratory outcomes:

Venapuncture (at least 7x in the first year): at every clinical visit -13, 0, 4, 8, 12, 16, 26, 39, 52 weeks.

The blood for erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP), complete blood count, leucocyte differentiation, ASAT, ALAT, LDH, BUN, Creatinine, total IgG, Rheumatoid factor, anti-CCP. Furthermore lymphocyte subpopulations will be analyzed using our FACS Canto machine and by their

cytokine production measured by Luminex as previously described by our own group: (effector and regulatory subpopulations: including CD19+, CD4+, CD8+lymphocytes and Th1-, Th2-, Th17-, FoxP3-Treg, IL10+-Treg phenotype). Detailed B cell activation markers: within the CD19 positive B-cell we will look for CD38+, CD86+, CD10+ , CD27+, sIgM, sIgD, sIgG en sIgA. With these markers we can assess the proportion of naïve, mature and memory cells. Serumcytokines will also be examined by Luminex (including IL1, IL6, IL12, IL17, IL23, TNFα, IFNγ, IL4, IL10).

Myeloid related proteins will be measured.

At last we will investigate the in vitro suppression by MSC and by T-regs of the proliferation of the stimulated PBMC. Supernatant of stimulated PBMC*s will be examined by Luminex.

Study description

Background summary

Juvenile Idiopathic Arthritis (JIA) is a frequent childhood disease with a prevalence of 1 per 1000 children. Arthritis and related conditions, such as JIA, cost the U.S. economy nearly $128 billion per year in medical care and indirect expenses, including lost wages and productivity. Its presentation, clinical course and response to treatment differ from its adult counter part Rheumatoid Arthritis (RA). Severe forms such as Systemic JIA and polyarticular JIA are associated with significant disability and loss of quality of life, as well as numerous side effects from chronic immune suppression, including corticosteroids. The introduction of the biological agents including blockers of TNF alpha-receptor, IL-1receptor and IL-6receptor have greatly improved the outcome. Annual costs of these biologics are around 11,000 Euro. However a proportion of these children remains refractory to all of these very expensive drugs. We were the first to show earlier that using another form of cellular therapy, autologous SCT, was effective in some 50% of such children, even after 8 years of follow up. It was associated with complications caused by the myeloablation and profound immunosuppression such as infections and fatal

haemophagocytosis.
Given the immunosuppressive effects of Mesenchymal Stromal Cells (MSC) and clinical responses observed in animal models and the current human studies in treatment of resistant graft versus host disease, diabetes, SLE and Rheumatoid Arthritis, application of allogeneic MSC is an attractive and safe option and may prove very relevant for this group with the poorest clinical outcome. As stated above patients with treatment resistant JIA have a severe disability and loss in quality of life and have often life long associated financial costs.
When effective, these young children retain their ability for schooling, work and social activities. Application of MSC is quite simple compared to haemopoietic stem cell transplantation. It can be performed as a short inpatient procedure and does not require hazardous treatment with myelo-ablative drugs. The current experience within the European Blood and Marrow Transplantation Group (EBMT) of more than 700 patients with aGVHD after allogeneic SCT show that allogeneic MSC infusion is safe. A systematic review of 8 RCTs including 321 patients with ischemic stroke, Crohn*s disease, cardiomyopathy, myocardial infarction, graft versus host disease, and healthy volunteers receiving intravascular (both autologous and allogeneic) MSC did not detect an association between acute infusional toxicity, organ systemic complications, infection, death or malignancy. There was a significant association between MSC and transient fever. Also in the 189 refractory RA patients who received allogeneic MSC, most adverse events were mild and transient (such as transient fever after infusion persisting for maximal 2 hours); there was only one patient who experienced a serious adverse event leading to discontinuation of the treatment.
Administering MSC to more Rheumatoid Arthritis patients will however not teach us more about the safety and efficacy in RF-negative JIA (>90% of all JIA) since from a pathophysiologic, clinical, therapeutic and prognostic view this is a totally different disease entity.
We believe that intravenous injection of MSC in therapy refractory JIA will be tolerated and will enable us to estimate the effect to plan for further studies.

Study objective

To find out if intravenous MSC is a safe treatment for children with therapy-resistant JIA

Study design

The study is a prospective patient-trial. The patient is it's own historic control regarding efficacy. regarding safety the controlgroup is the JIA-patients not treated with MSC as displayed by Pharmachild (a Pharmacovigilance database for JIA patients).

Week -13: Regular clinical visit: Study explanation and handing over study

information and informed consent forms.
Wk -12 Regular telephone call after 1week to discuss the lab results as usual and to ask about their opinion regarding the study and answering questions. If they agree to the study the signed and dated informed consent forms are send back to us in duplicate. Start of recording adverse events upon arrival of ICF.
Wk 0: regular clinical visit, MRI with contrast, venapuncture, MSC infusion
Wk 4: Extra clinical visit, venapuncture
Wk 8: Extra clinical visit, venapuncture, MRI and only if needed additional MSC iv
Wk 12: Regular clinical visit, venapuncture
Wk 16: Extra clinical visit with venapuncture and only if needed additional MSC iv
Wk 28: Stop recording mild adverse events (3 months after last possible MSC-infusion)
Wk 26+39: Regular outpatient clinical visits
Wk 52: Regular outpatient clinical visit, MRI; end of study

*The second or third MSC will only be given to those patients who initially met the ACR Ped 30 criteria but subsequently showed a loss of response before week 8 and/or 16.

Sample Size Calculation:
Using an 80% one-sided CI, it has been estimated that a pilot trial should have at least 9% of the sample size of the main planned trial (Cocks,K. & Torgerson,D.J. Sample size calculations for pilot randomized trials: a confidence interval approach. J. Clin. Epidemiol. 66, 197-201 (2013). Using the estimated effect size difference for the main trial and using a one-sided CI, this allows us to calculate a sample size for a pilot trial, which will make its results more useful than at present.
Looking at the trials leading to registration of new biologicals for the indication of JIA the number of biological allocated patients in the randomized phase contained 25 for etanercept , 68 for adalimumab and 60 for abatacept. Therefore we feel that if MSC were to be studied with an equal RCT in the near future, with 6 patients in this tolerability pilot study we fullfill the above mentioned requirements.

We chose the dose of 1 million MSC/kg body weight because it has been used widely as a dose for iv administration and doses of up to 160.8 million MSC even have been safely injected in human joints.

Intervention

MSC infusion (1-3x): MSC will be injected intravenously at a dose of 2 x 10E6 MSC/ per kg recipient body weight during 1 hour. There will be a 2 hour post-infusional observation period.
In case of beneficial but waning effect the administration of MSC can be repeated no earlier than 8 weeks after the former MSC infusion (week 8 or 16).

A maximum of 3 MSC infusions per patient is allowed.

Magnetic Resonance Imaging (MRI 3x): MRI will be performed 4 weeks before (wk0), 8 weeks (wk8) and 1 year after MSC injection (wk52)
Our local protocol is used for magnetic resonance imaging of large peripheral joints. Imaging will be performed with our Philips 3T scanner Gyroscan NT Intera, Philips Medical Systems, Best, The Netherlands using a flex-M coil. The following sequences are used: sagittal and coronal T1 TSE, sagittal T2 TSE, sagittal PD TSE, transverse T2 SPAIR and sagittal T1 SPIR with gadolinium iv. A contrast dose of 0.1 mmol/kg gadolinium (Gadovist®) is given if there are no known contra-indications (standardlist at our radiology department). MRI will be performed of a joint with blinding of the radiologist as to what treatment has been given.

Clinical visits (at least 9 times in the first year, which is 4 more times than for the typical JIA patient): -13, 0, 4, 8, 12, 16, 26, 39, 52 weeks
Thirteen weeks before first MSC infusion (wk -13), at the day of MSC-infusion and every 4 weeks thereafter for the first 4 months (wk 4, 8, 12 and 16). Further follow-up will be guided by patient complaints but at least every 13 weeks (wk26, 39 and 52). The visits will encompass complete medical history and monitoring for side effects. Furthermore complete physical examination including total joint count. Validated health and functionality related questionnaires (see below at outcome measures) will be provided to the parents/patients. Global assessments by the parents/patients measured with a 10-cm VAS.
Extensive physical examination will contain an evaluation of all joints as described previously. In short the joints will be assessed as being normal, warm, painful/tender, tender on passive motion, limited in motion. The degrees of passive motion will be noted for all limited joints. Global assessments by the physician measured with a 10-cm visual analogue scale (VAS)

Venapuncture (at least 7x in the first year instead of 4 times): at every clinical visit -13, 0, 4, 8, 12, 16, 26, 39, 52 weeks.
The blood will be analyzed during each clinical visit for erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP), complete blood count, leucocyte differentiation, ASAT, ALAT, LDH, BUN, Creatinine, total IgG, Rheumatoid factor, anti-CCP. Furthermore lymphocyte subpopulations will be analyzed by our FACS Canto machine and by their cytokine production measured by Luminex as previously described by our own group: (effector and regulatory subpopulations: including CD19+, CD4+, CD8+lymphocytes and Th1-, Th2-, Th17-, FoxP3-Treg, IL10+-Treg phenotype) Serumcytokines will also be examined by Luminex (including IL1, IL6, IL12, IL17, IL23, TNFα, IFNγ, IL4, IL10). At last we will investigate the in vitro suppression by MSC and by T-regs of the proliferation of the stimulated PBMC.

Study burden and risks

The burden of the participation is explained by the extra investigations when compared to standard treatment in a typical JIA patient. Although the included refractory patient will by definition not be the typical JIA patient we feel it is best to compare to the typical JIA patient in order to maximally discriminate the study procedures from regular care. Most likely the suitable patient (if not participating to this study) would have been regularly seen more than 4 times a year and would have had one or several MRI*s in such a year.
In our study during a period of 65 weeks there will be compared to typical JIA patients 3 additional clinical visits, 3 additional venapunctures (when possible combined with MSC infusion or MRI), 1-3x MSC infusions (1-hour infusion and 2-hour postinfusion observation), and 3 additional MRI*s with contrast infusion (always combined with venapuncture).
Regarding the visits however we must note that refractory polyarticular JIA patients included in this study already have failed abatacept which requires 4 weekly visits to our hospital for venapuncture and intravenous infusion. As for many unregistered biologicals that can be experimentally used in JIA (with uncertain outcome) such as ixekizumab, tocilizumab, brodalumab, golimumab the patient needs to come every 4 weeks to the hospital for their injection.
We must also stress that in very refractory JIA patients we sometimes need to make MRI*s with contrast every 3 months.
Compared to e.g. proceeding with autologous stem cell treatment or arthroplasty-surgery we feel that the burden of our protocol is minimal.

Risks of participation are negligible (low chance of mild harm).
Systematic review of literature shows so far that MSC treatment is safe in general and 196 RA patients as well. No association between acute infusional toxicity, organ systemic complications, infection, death or malignancy was detected. There was however a significant association between MSC and transient fever.
We have stringent release criteria for our MSC (see IMPD). Lastly we will use allogenic MSC which will be rejected more easily, thereby further reducing the risks for longterm side effects.
The possible benefit is that patients might have less pain, less limitations, better well-being, higher quality of life and a stem cell transplantation or life-long invalidity might be prevented. This might prevent serious morbidity and even mortality from SCT.
The study is group related since JIA is a unique disease that can only be tested in JIA patients since there is no adult disease similar enough to translate results from such a study to JIA patients without testing it in JIA. Indeed this is the case for many drugs that need to be tested in JIA first before they can be registered for JIA, not withstanding the results in RA. Rituximab and hydroxychloroquine for example are almost never used in JIA while they are registered for use in RA.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria: Patients (4-18 years of age) diagnosed with juvenile idiopathic arthritis according to the ILAR-criteria with active arthritis resistant to intra-articular steroids and systemic use of methotrexate and for whom no on-label indication exists for (not yet used) biologicals. The patient is followed for adverse events via the Pharmachild database. Signed informed consent by the patient and/or parent(s) or legal guardian(s)

Exclusion criteria

<4 or >18 years of age
Concurrent infection, febrile illness or malignancy.
Pregnancy.
Comedication: Biologic response modifiers.
Lack of written and verbal informed consent.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-10-2014
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO

Date:	18-09-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	30-01-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-08-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-002067-10-NL
CCMO	NL40454.000.13
Other	NTR TC=4146

Study results

Date completed:	11-01-2018
Actual enrolment:	6

Summary results
Trial is onging in other countries