Author’s response to reviews

Title: Dexamethasone implants in paediatric patients with noninfectious intermediate or posterior uveitis: First prospective exploratory case series

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Dear Dr. Carreno, dear Dr. Fonollosa Calduch, dear Dr. Anesi,

we sincerely thank Dr. Fonollosa Calduch and Dr. Anesi for their constructive and astute remarks, and comments to our manuscript!

With this letter we would like to answer to the questions and comments of the reviewer.

Reviewer 1:
Dear Dr. Fonollosa Calduch,

your totally right that 2 patients were 17 years old during study course and therefore young adults or adolescents. But uveitis was diagnosed at age 16 in our first patient and at the age of 15
years in our third patient. Both patients did not respond enough to systemic immunosuppressive
treatment so that they were treated off label in our study at age 17.

We used the term “paediatric patients” in some sentences because this is the term used by the
European Medicines Agency (EMA) for children from birth to less than 18 years.

Additionally we changed the title from “Dexamethasone implants in children with noninfectious
intermediate or posterior uveitis: First prospective exploratory case series.” to “Dexamethasone
implants in paediatric patients with noninfectious intermediate or posterior uveitis: First
prospective exploratory case series.”

And

“Children, 6 to 17 years old, with a vitreous haze score of ≥ 1.5+ or cystoid macular edema of >
300 µm could participate.” in the abstract/methods section to “Children and adolescents, 6 to 17
years old, with a vitreous haze score of ≥ 1.5+ or cystoid macular edema of > 300 µm could
participate.”

And

“Therefore, steroid-sparing agents are often applied earlier in children than in adults.” to
“Therefore, steroid-sparing agents are often applied earlier in children and adolescents than in
adults.”

and

“Methotrexate (MTX) is often the treatment of first choice in children with intermediate or
posterior uveitis, particularly if associated with juvenile idiopathic arthritis (JIA).” to
“Methotrexate (MTX) is often the treatment of first choice in paediatric patients with
intermediate or posterior uveitis, particularly if associated with juvenile idiopathic arthritis (JIA).”

and

“In such children and adolescents, an intravitreal steroid application may be effective.” to “In such children and adolescents, an intravitreal steroid application may be effective.”

and

“Systemic side effects appear to be absent, but the treatment has not been approved in children.” to “Systemic side effects appear to be absent, but the treatment has not been approved in paediatric patients.”

and

“To our knowledge this is the first prospective exploratory case series to evaluate DEX implants in children with uveitis.” to “To our knowledge this is the first prospective exploratory case series to evaluate DEX implants in paediatric patients with uveitis.”

and

“Our results as well as other studies indicate that DEX implants should be used with caution in children with known steroid response, glaucoma or other risk factors for glaucoma.” to “Our results as well as other studies indicate that DEX implants should be used with caution in paediatric patients with known steroid response, glaucoma or other risk factors for glaucoma.”
“The above mentioned studies may indicate that development of cataract occurs earlier in children than in adults.” to “The above mentioned studies may indicate that development of cataract occurs earlier in paediatric patients than in adults.”

and

“The results of our prospective exploratory case series suggest that intravitreal DEX implantation in children with idiopathic intermediate uveitis is effective in improving VA and decreasing inflammatory activity.” to “The results of our prospective exploratory case series suggest that intravitreal DEX implantation in paediatric patients with idiopathic intermediate uveitis is effective in improving VA and decreasing inflammatory activity.”

We really understand your concerns about the small sample size of our case series. Five to 10 paediatric patients were planned, but due to the low incidence rate of intermediate uveitis in paediatric patients and the strict in- and exclusion criteria of our study it was really difficult to find patients, who met the inclusion criteria. So we stopped the study to plan a multicenter study based on our primary results and study design. It would be really important to publish this case series to apply for further funding and to continue the study in a multicenter study design. As seen in the literature there is a need for a prospective well designed study with strict in- and exclusion criteria to receive clear results. The value of our work can be seen as well in reaching ethics and BfArM approval which took an amount of work, organisation and costs. Additionally e-CRF was created by myself. Ethics application (70 pages), BfArM application and e-CRF are available. So it should be easy to plan a multicenter study based on this preliminary work, which could probably lead to an approval extension for DEX implants in paediatric patients.

The EMA encourages studies in pediatric patients through the Paediatric Regulation.

It is written on the website that the objective of the Paediatric Regulation is to improve the health of children in the European Union (EU):
• facilitating the development and availability of medicines for children from birth to less than 18 years

• ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately

• improving the availability of information on the use of medicines for children

Our study was registered under the European Union Drug Regulating Autorities Clinical Trials (EudraCT) - nr: 2013-000541-39 and so we think that it would be of general interest to publish our findings. We really hope for your consent!

Reviewer 2:

Stephen Anesi (Reviewer 2):

Dear Dr. Anesi,

we followed your suggestions and changed:

1. Abstract - I would be careful to say that this data suggests IOP rises are seen "more often" in pediatric patients given the low n, rather I would say this study confirms IOP rises may also occur in the pediatric population and should be monitored and treated appropriately.”

to abstract: conclusions: “This study confirms that IOP rises may also occur in the pediatric population and should be monitored and treated appropriately.”
This point is again raised in the discussion, and the authors state it is not clear why there is a
difference in the % of patients who have IOP rises, and again, the low n makes this.

We deleted: “The reason for this difference is not clear.” in the discussion and replaced the
sentence by “This may be due to the low number of patients included in our study.”

2. Background - MTX is often the first choice, recommend avoiding absolutes in statements like this.

We changed “Methotrexate (MTX) is the treatment of first choice in children with intermediate
or posterior uveitis, particularly if associated with juvenile idiopathic arthritis (JIA)” to
“Methotrexate (MTX) is often the treatment of first choice in paediatric patients with
intermediate or posterior uveitis, particularly if associated with juvenile idiopathic arthritis
(JIA)” in the introduction.

3. Patient 2 - Mentions he is 9, chart says 8 years old. Please adjust for consistency.

Sorry about this! The patient was 9 years old. This was changed in the chart.

4. Patient 3 - Would like to know how long the patient remained stable on the reduced dose of
MTX.

I would like to see some comment on expected course of disease after the 6 month treatment
period, given the attempted decrease in systemic therapy, especially considering many readers
would expect recurrent disease at 6 months after the implant wears off.
Patient 1: We described the disease course after study completion: “After study completion the intraocular inflammatory activity increased again but the patient wished no further DEX insertion so that the immunosuppressive therapy was augmented consecutively to CSA 6.25mg/kg body weight daily, Decortin 0.15mg/kg body weight daily and MTX 10.34 mg/m2/orally once weekly. Actually the systemic therapy was changed to Adalimumab 40mg subcutaneously every 2 weeks and MTX 10.34 mg/m2/orally once weekly and the intraocular inflammation is controlled with this regimen. VA accounts for 75 ETDRS letters.“

Patient 2: „During the following year VA stayed stable and VH score increased slightly to 0.5+ units.” was already written. We further inserted: “One year after study completion a relapse occurred and could be controlled fast with steroid pulse therapy. Actually the intraocular inflammation is quiet without any therapy and VA of 80 ETDRS letters.”

Patient 3: “After study completion disease activity remained stable with therapy of oral MTX 6.25 mg/m2/once weekly with stable VA of 79 ETDRS letters, CRT and IOP 2.5 years after study completion.” was already written. We completed to: “After study completion disease activity remained stable with therapy of oral MTX 6.25 mg/m2/once weekly with stable VA of 79 ETDRS letters, CRT and IOP 2.5 years after study completion.”

We included: “But the treatment effect hold on in patient 2 for 1 year and in patient 3 with reduced systemic therapy for 2.5 years after study completion up to date.” in the first chapter of the discussion.

and “The effect may last much longer than 6 months and reduction of systemic therapy may be possible in some cases.” into the conclusions of the discussion.

Overall nicely done.

Thank you so much for the encouraging comment!!!

No controls were necessary, nor would controls be ethical in this study.
We hope that we could answer your questions to your satisfaction. Otherwise please do not

With kind regards
Sincerely
Yours
Sibylle Winterhalter and Co-authors