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Associating adalimumab with methotrexate decreases uveitis associated with juvenile idiopathic arthritis

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English key words: adalimumab, arthritis, juvenile: uveitis, methotrexate, anti-inflammatory, agents.
Spanish key words: adalimumab, artritis juvenil, uveítis, metotrexato, antiinflamatorios.

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Associating adalimumab with methotrexate decreases uveitis associated with juvenile idiopathic arthritis

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Abstract

Authors' conclusions: adalimumab, added to the usual therapy with methotrexate, achieves significantly better control of juvenile idiopathic arthritis associated with uveitis in children and adolescents, although the rate of side effects is much higher with this drug.

Reviewers' commentary: with the available data, associating adalimumab to methotrexate seems effective for the treatment of uveitis associated with juvenile idiopathic arthritis in children and adolescents, but the described adverse events and costs should be taken into account and should be used with caution.

Key words: adalimumab, arthritis, juvenile: uveitis, methotrexate, anti-inflammatory, agents.

Asociar adalimumab a metotrexato disminuiría la uveítis asociada a la artritis idiopática juvenil

Resumen

Conclusiones de los autores del estudio: adalimumab, añadido a la terapia habitual con metotrexato, logra un control significativamente mejor de la uveítis asociada a artritis idiopática juvenil en niños y adolescentes, aunque la tasa de efectos secundarios es mucho más alta con este fármaco.

Comentario de los revisores: con los datos disponibles, asociar adalimumab al metotrexato parece efectivo para el tratamiento de la uveítis asociada a artritis idiopática juvenil en niños y adolescentes, pero los eventos adversos descritos y los costes deben ser tomados en cuenta y se debería utilizar con precaución.

Palabras clave: adalimumab, artritis juvenil, uveítis, metotrexato, antiinflamatorios.

STRUCTURED ABSTRACT

Objective: to assess the efficacy of the monoclonal antibody adalimumab (ADM) in the treatment of juvenile idiopathic arthritis-associated uveitis (JIA-U).

Design: multicentre double-blind randomised controlled trial.

Setting: 14 ophthalmology or rheumatology clinics in the United Kingdom (Bristol, Liverpool and London).

Trial population: adolescents and children aged more than 2 years with a diagnosis of active JIA-U that had been receiving stable treatment with methotrexate (10 to 20 mg/m^2 of body surface area, maximum of 25 mg) for at least 3 months. The exclusion criteria were previous exposure to ADM or other biologic agents, receipt of more than 6 topical glucocorticoid drops per eye per day, and treatment with prednisone (or the equivalent) at a dose exceeding 0.2 mg/kg of body weight per day.

Intervention: between October 2011 and April 2015, out of 332 eligible patients, 242 were finally excluded because they did not meet the criteria. Sixty patients were randomly assigned to the group that received ADM (intervention group [IG]) via the subcutaneous route and every two weeks (at a dose of 20 mg in patients weighing less than 30 kg, or a dose of 40 mg in patients weighing 30 or more kg), and 30 patients to receive placebo (control group [CG]), which was also injected every 14 days. Fifteen percent of patients in the IG and 23% in the CG withdrew from the trial intervention for reasons other than treatment failure.

Outcome measurement: the primary endpoint was the time to treatment failure (assessed by determination of the grade of intraocular inflammation by slit-lamp biomicroscopy applying well-defined criteria). Ophthalmic assessments were performed at the time of randomisation and during scheduled visits at 4, 8 and 12 weeks and every 3 months thereafter until completion of 18 months of treatment or withdrawal from treatment, with a followup of six months in all patients after treatment completion or withdrawal. All patients that received at least 1 dose of ADM or placebo were included in the safety analyses (total adverse events and total severe adverse events). The statistical analysis was by intention to treat and primarily assessed the time to treatment failure by plotting Kaplan-Meier survival curves, comparing groups with the long-rank test and fitting a Cox proportional-hazards model. A sensitivity analysis tested the effects of missing data, participants who stopped the intervention protocol early, or participants that were incorrectly identified as having treatment failure.

Main results: the trial was stopped early owing to evidence that the risk of treatment failure was significantly lower in the IG compared to the CG (treatment failure in 27% compared to 60% of patients, respectively; hazard ratio [HR] of the IG versus CG of 0.25; 95% confidence interval [95 CI]: 0.12 to 0.49). Nine sensitivity analyses confirmed the conclusions of the primary analysis. There were differences in the adverse events experienced by each group: the rate of serious adverse events was greater in the IG (0.29 serious events graves per patient-year [95 CI: 0.15 to 0.43]) compared to the CG (0.19 events per patient-year [95 CI: 0.00 to 0.40]); the total number of events per patient-year was significantly greater in the IG (10.07; 95 CI: 9.26 to 10.89) compared to the CG (6.51; 95 CI: 5.26 to 7.77).

Conclusion: combining ADM with methotrexate seemed useful for the treatment of JIA-U, despite the significant increase in the incidence of adverse events (most of them mild).

Conflicts of interest: detailed in the full text of the article.

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COMMENTARY

Justification: anterior uveitis, inflammation of the iris, choroid, or ciliary body, can cause significant eye morbidity, including loss of vision. In the paediatric age group, the most common underlying diagnosis is juvenile rheumatoid arthritis. Most studies on monoclonal antibody therapy have been performed in the adult population, and the study reviewed here is relevant in that it focuses on children with JIA-U.[1]

Validity or scientific rigour: the research question was very specific, the only disease in the included patients was JIA-U, and their random assignment was correct. When it came to outcome measurement, they used an assessment tool for uveitis that has not been validated in children, but is endorsed by international consensus guidelines. The followup was too short for the detection of adverse events in the long term. The trial was stopped early on the basis of appropriate boundaries that were predefined in the protocol. The results can only be generalised to the population of patients with JIA-U treated with methotrexate and ADM.

Clinical relevance: the risk of treatment failure in the CG compared to the IG (HR of treatment failure in IG versus CG: 0.25; 95 CI: 0.12 to 0.49) is very high for the variable of treatment efficacy. The number needed to treat (NNT) to avoid 1 treatment failure was 6 (95 CI: 5 to 8)*. This drug has not proven as useful in studies conducted in adults.[2] The trial was stopped before reaching the recruitment target, although the circumstances under which it ought to be stopped were predefined; nevertheless, this development may lead to overestimation of treatment effects and limits the duration of followup.[3] The effectiveness of ADM decreases over time, and there was a significant incidence of adverse events in this study, with an average of 1 out of every 10 patients with JIA-U treated with ADM in combination with methotrexate experiencing a serious adverse event, and 1 out of 3 experiencing 1 adverse effect of any kind.[4]

Applicability to clinical practice: the available data indicate that ADM is an effective drug in the treatment of JIA-U in combination with methotrexate. However, the described adverse events and costs should be taken into account, and it should be used with caution based on the results of this study.

Conflicts of interest: the authors of the commentary have no conflicts of interest to declare.

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* Calculated by authors of the commentary from data in original article.