**Outcome of patients with juvenile idiopathic arthritis on biological therapy and varicella-zoster virus infection**

Evolución de pacientes con artritis juvenil en terapia biológica e infección por virus Varicela Zoster. A propósito de 4 casos

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**Abstract**

**Introduction:** Varicella virus infection may evolve into severe disease in immunocompromised children. There are few studies that describe the clinical presentation of varicella infection in patients with Juvenile Idiopathic Arthritis when on biological therapy. **Objective:** Describe the outcome of patients diagnosed of Juvenile Idiopathic Arthritis, who acquired a varicella virus infection during treatment with biological therapy. **Clinical cases:** A description is presented on 4 cases of Juvenile Idiopathic Arthritis in children between 3 and 12 years old, who developed a varicella-zoster infection during treatment with different biological therapies. Two patients were under treatment with anti-TNF agents, one treated with Anti IL-6 agent, and one patient a T cell costimulatory blockade agent. Two of them received varicella vaccination prior to the start of biological therapy. All of them received different therapies and had favourable outcome without developing complications. No significant differences were found as regards the type of biological therapy or history of previous vaccination. Biological therapy was suspended for at least 2 weeks in all patients, and was restarted without reactivation of arthritis. **Conclusions:** No serious complications were observed in this patient series of children with JIA treated with biological therapy associated with VZV infection.

**Introduction**

The varicella zoster virus (VZV) belongs to the herpes viridae family. Its primary infection causes chickenpox, and its reactivation gives rise to herpes zoster. Chickenpox is a common childhood disease and its course is usually benign and self-limited in the immunocompetent host. After the first infection is acquired, VZV remains latent in the sensory nodes of the dorsal roots and cranial nerves, and may present intermittent periods of reactivation such as herpes zoster, which significantly increase with age and immunosuppression.

The seroprevalence for VZV in different studies is
Clinical cases

Case 1
Male patient, diagnosis of extended oligoarticular JIA ANA (+). Rheumatoid factor (-) HLA-B27 (-), diagnosed at 3 years. He was treated with intra-articular corticosteroids at the initial stage and then with methotrexate. At 7 years of age, he presented refractory chronic bilateral uveitis to topical treatment, initiating biological therapy with adalimumab (anti-TNF-α).

After 6 months of biological therapy, there was a picture of isolated vesicular lesions, without fever, without irritability nor compromise in his general condition. He was evaluated on an outpatient basis in rheumatology, as a varicella-compatible condition, so it was decided to hospitalize him for intravenous treatment. He had a history of vaccination against varicella at 3 years of age, prior to the start of the immunosuppressive treatment. Treatment with acyclovir was indicated and the antirheumatic therapy was temporarily discontinued. It presented good evolution, so it was changed to oral acyclovir until completing 10 days.

Case 2
Female patient, psoriatic JIA diagnosed at 2 years of age. Due to her arthritis of severe evolution she received combined treatment with prednisone, sulfasalazine and methotrexate in full doses. After 3 years of treatment, due to insufficient response, biological therapy with etanercept (anti-TNF-α) was added. After 9 years of disease, active arthritis persisted, and the patient switched from biological therapy to a second anti-TNF-α, using adalimumab, with no response within 4 months of use. Because of the above, it was changed to a third biological therapy, abatacept (T-cell costimulatory inhibitor).

After 4 months of abatacept initiation she presented skin lesions typical of varicella. After 24 h a compromise of the general condition was added, fever and extension of lesions to the trunk and oral mucosa. She had not received immunization against chickenpox. Varicella was clinically confirmed and she was hospitalized for treatment with intravenous acyclovir; Base therapy was discontinued. Treatment with cefazolin was added on suspicion of overinfection with favorable evolution. She received 5 days of intravenous acyclovir and 2 days of oral therapy.

Case 3
Male patient with systemic polyarticular JIA, diagnosed at 2 years of age. He received treatment with methotrexate and high doses of prednisone with poor response. After a year of evolution, biological therapy with tocilizumab (anti IL-6) was initiated and it was possible to discontinue corticosteroids.

After 9 months of treatment with tocilizumab he presented a picture compatible with varicella. After 24 h a compromise of the general condition was added, fever and extension of lesions to the trunk and oral mucosa. He had not received immunization against varicella due to the severity of arthritis at the time of diagnosis, requiring immediate rheumatologic treatment. Previous serology had been requested for VZV, with negative result.

Case 4
Female patient, extended oligoarticular JIA ANA (+), FR (-), HLA B 27 (-), diagnosed at one year and 9 months of age. She received treatment with intra-articular corticosteroids and then, due to the increase of the number of involved joints, methotrexate was added. At 4 years of age, due to insufficient response,
etanercept was added, and the prednisone was withdrawn.

At 6 years of age, she presented varicella, evaluated in the Emergency Department, where symptomatic therapy (antihistamine and paracetamol) was indicated. She did not consult with the rheumatologist pediatrician. The parents discontinued the anti-TNF therapy for 3 weeks. She evolved without complications. This patient had received the varicella vaccine.

Clinical cases are summarized in table 1.

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age at diagnosis JIA (years)</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>One year, 10 months</td>
</tr>
<tr>
<td>Type JIA</td>
<td>Oligoarticular+uveitis</td>
<td>Psoriatic</td>
<td>Systemic</td>
<td>Extended oligoarticular</td>
</tr>
<tr>
<td>Varicella vaccine</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Basic therapy</td>
<td>Methotrexate</td>
<td>Methotrexate+ sulfazalazine+ prednisone</td>
<td>Methotrexate</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Biological therapy</td>
<td>Adalimumab</td>
<td>Abatacept</td>
<td>Tocilizumab</td>
<td>Etanercept</td>
</tr>
<tr>
<td>Age at diagnosis of Varicella (years)</td>
<td>7</td>
<td>12</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Latency between biological therapy and Varicella (months)</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Yes, 5 days preventive</td>
<td>Yes, 5 days preventive</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Antiviral treatment</td>
<td>Aciclovir 5 days IV and 5 days VO</td>
<td>Aciclovir 5 days IV and 2 days VO</td>
<td>Aciclovir oral route for 7 days</td>
<td>No</td>
</tr>
<tr>
<td>Clinical picture of Varicella</td>
<td>No fever, mild disease progression</td>
<td>Febrile, moderate progression lesion, superinfection</td>
<td>No fever, rare skin lesions</td>
<td>No fever, moderate progression lesion</td>
</tr>
<tr>
<td>Complications</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

JIA: juvenile idiopathic arthritis.

Discussion

Four patients with JIA, aged 3 to 12 years old, who had varicella with different biological therapies are described, (2 with anti-TNF-α, one with anti-IL-6 and the other with T-cell co-stimulation blocker). Only 2 children had received active immunization, both with oligoarticular JIA and who at the beginning of the disease had only used intra-articular corticoid therapy, which did not contraindicate the vaccine. The diagnosis of varicella was clinical, so no serological confirmation was required.

The latency between the presentation of varicella and the beginning of the biological therapy varied between 6 months and 7 years. The 4 children were receiving methotrexate concomitantly. In case 2 the patient also received sulfazalazine, prednisone and had previously received 2 different anti-TNF-α biological therapies. Only 4 months prior to varicella it had changed to the inhibitor of T-cell costimulation, which is associated with a lower risk of infections. All of them evolved favorably, without complications.

Adult patients with rheumatoid arthritis who started methotrexate or anti-TNF-α would have a similar risk of opportunistic infections, with a relative risk of 1.46 and 1.25 respectively.

The treatment for varicella was quite varied, since there is no specific recommendation in patients with biological therapy. In patients who are immunosuppressed, treatment with parenterally acyclovir (30 mg/kg/day or 1,500 mg/m²/day for 7 to 10 days) is recommended as early as possible, and its efficacy is maximal if it is started before 24-48 h after the onset of the rash. In children it is possible to change to oral acyclovir after 2 days of evolution without the appearance of new lesions.
The 2 cases that were hospitalized were decided as a preventive measure, and following the suggestions for immunosuppressed patients, not by the severity of the disease. There is a lack of data to support treatment behavior, since there is insufficient information on the severity of varicella with these therapies. Because of the above, we believe that based on the data available to this date, it is not possible to make a general suggestion at institutional level. What we do is suggest to inform the parents of the possible risks of suffering from chickenpox when using biological therapy, advise them to consult the pediatric rheumatologist at an early stage when there is suspicion of the disease or there is a history of contact with VZV and they should indicate the use of oral or parenteral acyclovir, evaluating the severity of the disease and the degree of associated immunosuppression.

In all cases, biological therapy was discontinued for at least 2 weeks from the time of varicella diagnosis, and this was not associated with reactivation of arthritis. Some authors have suggested that, in mild cases, treatment could be restarted after complete resolution of the lesions. 

A study in adults with rheumatoid arthritis and anti-TNF-α therapy showed a 1.82-fold higher risk of presenting VZV with respect to the use of disease-modifying antirheumatic drugs, in many cases of severe presentation requiring hospitalization. Lesions have also been found in patients with adalimumab. The BIOBADASER 2.0 study in adults with rheumatic diseases exposed to anti-TNF-α concludes that these patients have a 10-fold increased risk of hospitalization due to VZV infections than the general population. This analysis does not allow differentiation if this is due only to the use of anti-TNF-α or the underlying diseases or other immunosuppressive drugs also exercise influence.

In addition, in adults, the majority of diseases or other immunosuppressive drugs also exert influence. In our patients a dose had been administered, between 3 and 4 years prior to infection. Some authors have pointed out that the immunity of the varicella vaccine decreases with time. The annual rate of chickenpox in vaccinated people increases with the time passed since vaccination, from 1.6 to 9 cases per 1,000 people per year. The use of a second dose of the vaccine is proposed for a better immunity. The recommendation of the American Academy of Pediatrics is to administer 2 doses of the vaccine from the year of age separated by at least 3 months (first dose between 12 and 15 months, second dose between 4 and 6 years), and in children aged 13 years and older it is suggested to administer 2 separate doses for at least 28 days. The use of the vaccine would reduce the incidence of herpes zoster.

The clinical cases described represent the total number of children with varicella since biological therapy was available in our hospital since July 2009. The total number of children with biological therapy is 27, with a follow-up period of 6 years. It would be very useful to carry out a prospective study in pediatric patients with biological therapy, since until this date most of the published data of adverse effects and opportunistic infections have been performed in the adult population.

Conclusion

Pediatric patients with JIA who are treated with biological therapy are at risk of presenting opportunistic infections such as VZV, despite being previously vaccinated. In this series of patients of JIA children treated with biological therapy who underwent VZV infection no serious complications were observed. In these patients, the therapy was temporarily suspended and subsequently resumed without observing reactivation of the disease.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.
References