References

1. Gallego Riestra S, Riaño Galán I. ¿Quién decide qué datos deben constar en la historia clínica en relación con el origen biológico? Aten Primaria. 2018;50:74–8.
2. Harper JC, Geraedts J, Borry P, Cornel MC, Dondorp WJ, Gianaroli L, et al. Current issues in medically assisted reproduction and genetics in Europe: Research, clinical practice, ethics, legal issues and policy: European Society of Human Genetics and European Society of Human Reproduction and Embryology. Hum Reprod. 2014;29:1603–9.
3. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open. 2017;7:e016461.
4. Tada H, Hosomichi K, Okada H, Kawashiri MA, Nohara A, Inazu A, et al. A de novo mutation of the LDL receptor gene as the cause of familial hypercholesterolemia identified using whole exome sequencing. Clin Chim Acta. 2016;453:194–6.
5. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5 Suppl 3:S1–8.
6. Enguer P, Ramón F. Dilemas bioéticos y jurídicos de la reproducción asistida en la sociedad actual en España. Revista Latinoamericana de Bioética. 2017;18:104–35.

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Rapid desensitisation to tocilizumab in systemic idiopathic juvenile arthritis☆

Desensibilización rápida a tocilizumab en artritis idiopática juvenil sistémica

To the Editor:

Systemic juvenile idiopathic arthritis (SJIA) accounts for 10%–15% of cases of juvenile idiopathic arthritis (JIA), with a similar incidence in individuals of either sex. In 66% of patients, it has onset before age 5 years, a subset that includes the most severe cases and in which extraarticular manifestations are particularly important.[1]

The advent of monoclonal antibodies against human interleukin 1 (IL-1) and 6 (IL-6) (tocilizumab) revolutionized the treatment of SJIA, achieving remission in cases refractory to conventional treatment.[2] Tocilizumab is a well-tolerated drug. Adverse reactions following its administration have been described in 8% of patients treated with the drug, of which 0.13% were hypersensitivity reactions.[3,4]

We present the case of a female patient aged 2 years with a body weight of 10 kg that presented with persistent high-grade fever of up to 40 °C of 3 weeks' duration, a generalised erythematous maculopapular rash that worsened during febrile episodes and resolved spontaneously, axillary, inguinal and cervical lymph enlargement with mobile, soft and painless enlargement to 2 cm, arthritis in the knees, elbows and hands manifesting with pain and impaired gait and hepatosplenomegaly. Blood tests revealed hypoalbuminaemia, hypochromic microcytic anaemia, leucocytosis and elevation of liver enzymes, and after exclusion of underlying infection or blood or solid tumours, SJIA was diagnosed based on the criteria established by the International League of Associations for Rheumatology.

The patient started treatment with methotrexate, oral prednisone and intravenous boluses of methylprednisolone, but subsequently developed macrophage activation syndrome, with elevation of serum ferritin levels (14 060 ng/mL), a sharp decrease in the erythrocyte sedimentation rate, thrombocytopenia, anaemia and elevation of transaminases and lactate dehydrogenase, which required initiation of treatment with tocilizumab, administered in doses of 12 mg/kg for a total dose of 120 mg every 15 days. The patient did not exhibit hypersensitivity reactions to the first cycle of tocilizumab, but she continued to exhibit clinical and laboratory features suggestive of persistent disease activity. Following consultation with the department of haematology, etoposide was administered, but it did not achieve clinical improvement.

In the first 5 min of infusion of the second cycle of intravenous tocilizumab, the patient developed a rash, facial swelling, tachycardia, tachypnoea, difficulty breathing, oxygen desaturation to 88%, abdominal pain, fever and piloerection, leading to discontinuation of the bolus of tocilizumab and administration of intramuscular

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Table 1 Tocilizumab desensitization protocol in 8 steps.

Step	Time (min)	Infusion mL/h (drip)	Infused volume	Percent infused	Infused dose (mg)	Cumulative dose (mg)
1	15	0.8 mL	0.2 mL	0.0625%	0.096 mg	0.096 mg
2	15	1.6 mL	0.4 mL	0.125%	0.192 mg	0.288 mg
3	15	3.2 mL	0.8 mL	0.25%	0.384 mg	0.672 mg
4	15	6.4 mL	1.6 mL	0.5%	0.768 mg	1.44 mg
5	15	12.8 mL	3.2 mL	1%	1.536 mg	2.976 mg
6	15	25 mL	6.3 mL	2%	3.024 mg	6 mg
7	15	50 mL	12.5 mL	4%	6 mg	12 mg
8	135	100 mL	225 mL	92%	108 mg	120 mg
Total time: 4 h, infused volume: 250 mL						

h, hour; min, minutes.

adrenaline, corticosteroids and intravenous antihistamines, which achieved resolution of the symptoms.

The patient underwent a skin prick test with tocilizumab at a 20 mg/mL concentration, which turned out positive (papule of 7 × 6 mm compared to 1 × 1 mm with the glycerine solution negative control). Due to the severity of symptoms, the lack of alternative treatments and the efficacy of tocilizumab, we initiated a sequential rapid desensitization protocol in 8 steps (Table 1) with a solution of tocilizumab with a concentration of 0.47 mg/mL made by dissolving 6 mL of tocilizumab (200 mg/10 mL) in 250 mL of physiological saline 0.9%. The patient was premedicated with intravenous chlorpheniramine IV (0.15 mg/kg) and intravenous methylprednisolone IV (1 mg/kg) una 1 h before starting the protocol.

The protocol was successful, and the patient did not develop immediate and/or delayed hypersensitivity reactions, and the protocol was repeated every 2 weeks for a total of 9 cycles of intravenous tocilizumab. Unfortunately, the administration of the monoclonal antibody did not achieve disease remission, and following consultation with the department of haematology, the patient underwent a haematopoietic stem cell transplantation, the outcomes of which were excellent. At present, the patient is in remission and in follow-up by the department of rheumatology.

The evidence on the management of hypersensitivity reactions to tocilizumab in the paediatric age group is scarce compared to the evidence in adults.[5] Due to advances in treatment, monoclonal antibodies have become a cornerstone of treatment in rheumatological, oncological and chronic inflammatory diseases.[6]

Ours is the first description of rapid desensitization of a paediatric patient in the Latin American population. Although this posed a therapeutic challenge due to the age of the patient and the difficulty of recognizing symptoms of anaphylaxis, we were able to deliver the protocol successfully, an intervention that was necessary due to the lack of an alternative treatment.

References

1. Blanco de la Portilla LE, Basanta Ampudia R, Blanco de la Portilla MC. Síndrome de activación macrofágica en paciente pediátrico con enfermedad de Still. Univ Méd Pinaren˜a. 2019;15:155–62.
2. Soyer O, Demir S, Bilginer Y, Batu ED, Sonmez HE, Arıcı ZS, et al. Severe hypersensitivity reactions to biological drugs in children with rheumatic diseases. Pediatr Allergy Immunol. 2019;00:1–8.
3. Demir S, Soyer O, Bilginer Y, Sag E, Sahiner UM, Buyuktiryaki B, et al. Desensitisation overcomes rituximab- and tocilizumab-related immediate hypersensitivity in childhood. Clin Exp Rheumatol. 2019;00:1–6.
4. Castells M. Drug hypersensitivity and anaphylaxis in cancer and chronic inflammatory diseases: The role of desensitizations. Front Immunol. 2017;8:1–11.
5. Justet A, Neukirch C, Poubeau P, Arrault X, Borie R, Dombret MC, et al. Successful rapid tocilizumab desensitization in a patient with Still disease. J Allergy Clin Immunol Pract. 2014;2:631–2.
6. Akarsu A, Soyer O, Sekerel BE. Hypersensitivity reactions to biologicals : from bench to bedside. Curr Treat Options Allergy. 2020;00:1–13.

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