Biological drugs in paediatric COVID-19 infection: what patients, which drug, how much and how long

Sirs,

We read with interest the "Mortality in tocilizumab-treated patients with COVID-19: a systematic review and meta-analysis" by Berardicurti *et al*. (1) reporting encouraging data about the use of tocilizumab in severe forms of COVID-19 infection. These patients presented a clinical picture characterised by severe pulmonary involvement and hyperinflammatory state deriving from the development of a cytokine storm syndrome. The treatment with an interleukin 6 (IL-6) inhibitor led to a mortality decrease in the group at higher risk to the same level of patients with a mild disease.

Considering the paediatric setting, infants and children seem to have a lower susceptibility to SARS CoV-2, reporting mild or no symptoms. However, the onset of a multisystemic inflammatory syndrome in children (MIS-C) a condition characterised by fever, inflammation, and multiorgan dysfunction, late occurring during the course of SARS-CoV-2 infection, may represent a life-threatening condition requiring the prompt use of biological drugs together with intensive-care support.

To this regard, three consensus guidelines by the United Kingdom PIMS-TS National Consensus Management Study Group (2), by the American College of Rheumatology (ACR) (3) and the Paediatric Section of the European Society of Emergency Medicine and European Academy of Paediatrics (4) provided recommendations about the management MIS-C patients. All the statements derived from expert opinion, clinical experience and data borrowed from similar hyperinflammatory conditions of the paediatric age since no results from randomised controlled trials are available. All the clinical guidelines highlight the prominent role of a multidisciplinary team composed of paediatric infectious diseases experts, immunologists, rheumatologists and paediatric cardiologists and intensivists for the management of MIS-C. Moreover, a stepwise immunomodulatory treatment is proposed, and intravenous immunoglobulin and glucocorticoids are considered the first- and second-line agents, respectively. The type of therapy and its initiation should be modulated based on the patient's clinical conditions at the first evaluation. Therefore, children with a severe presentation may benefit from early initiation and from a more aggressive treatment approach even if the full diagnostic process is not still completed. In the case of refractory disease, the panels of experts appear to agree on the need to promptly introduce a biological therapy, but a unique consensus on the drug of choice, between tocilizumab, anakinra and infliximab, has not been reached.

To our knowledge, up to October 2020, there have been 37 papers reporting the use of biological therapy for the treatment of MIS-C: 14 case reports and 23 case series with a total of 754 patients of whom 164 undergoing a biological drug. Previous adopted drugs were anakinra in 80 patients, tocilizumab in 69 cases, infliximab in 17 subjects and rituximab in 2 cases (Table I). These therapeutic approaches proved effective in almost all cases (96.3% data available in 82 patients), although dose, administration route and duration therapy were rarely specified.

The ACR consensus guidelines suggest tapering the immunomodulatory therapy for a period of 2–3 weeks in order to prevent a rebound of the inflammatory state. In this perspective, biological drugs may prove useful in maintaining a balance even in the subacute phase of MIS-C and acting as a steroid-sparing agent. At the moment, the scales seem to be tipping equally in favour of tocilizumab and anakinra, but no head-to-head comparisons are available. Further studies are advocated in order to clarify which of the two drugs appears most appropriate and at which dosage and administration route both as acute phase treatment and as maintenance therapy.

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Table I. Studies reporting biological therapy in MIS-C treatment.

Author, year	Type of study	n. of patients	n. of patients treated with biological drugs	Anakinra	Tocilizumab	Infliximab	Rituximab	Recovery with biologic treatment
De Lama Caro Paton, 2020	Case series	12	8	1	7	0	0	8/8
Orlanski Meyer, 2020	Case report	1	1	1	0	0	0	1/1
Mc Culloch, 2020	Case report	1	1	0	1	0	0	1/1
Kaya Acka, 2020	Case series	3	2	1	1	0	0	1/2
Ouldali, 2020	Case series	8	1	0	1	0	0	1/1
Belhadjer, 2020	Case series	35	3	3	0	0	0	3/3
Derespina, 2020	Case series	70	4	1	3	0	0	4/4
Davies, 2020	Case series	78	17	8	3	7	1	NA
Kaushik, 2020	Case series	33	16	4	12	0	0	NA
Lee, 2020	Case series	28	5	5	0	0	0	5/5
Feldstein, 2020	Case series	186	38	24	14	0	0	NA
Pouletty, 2020	Case series	16	2	1	1	0	0	2/2
Whittaker, 2020	Case series	58	11	3	0	8	0	NA
Balasubramanian, 2020	Case report	1	1	0	1	0	0	1/1
Velasco Puyo, 2020	Case report	1	1	0	1	0	0	1/1
Abdel-Mannan, 2020	Case series	4	2	2	0	0	1	2/2
Cheung, 2020	Case series	17	1	0	1	0	0	1/1
Chiotos, 2020	Case series	6	1	1	0	0	0	1/1
Greene, 2020	Case report	1	1	0	1	0	0	1/1
Grimaud, 2020	Case series	20	2	1	1	0	0	2/2
Hutchinson, 2020	Case report	1	1	1	0	0	0	1/1
Miller, 2020	Case series	44	8	8	0	0	0	8/8
Riollano-Cruz, 2020	Case series	15	14	2	12	0	0	13/14
Rodriguez Gonzales, 2020	Case report	1	1	0	1	0	0	1/1
Shenker, 2020	Case report	1	1	1	0	0	0	1/1
Waltuch, 2020	Case series	4	4	1	4	0	0	4/4
Kest, 2020	Case series	3	1	0	1	0	0	1/1
Riphangen, 2020	Case series	8	1	0	0	1	0	1/1
Dolinger, 2020	Case report	1	1	1	0	0	0	1/1
Torres, 2020	Case series	27	2	0	2	0	0	2/2
Prashant, 2020	Case series	33	3	3	0	0	0	3/3
Choi, 2020	Case series	32	4	4	0	0	0	4/4
Al Ameer, 2020	Case report	1	1	1	0	0	0	0/1
Mahajan, 2020	Case report	1	1	1	0	0	0	1/1
Alnashri, 2020	Case report	1	1	0	1	0	0	1/1
Abel, 2020	Case report	1	1	1	0	0	0	1/1
Domico, 2020	Case report	1	1	0	0	1	0	1/1
Total number		754	164	80	69	17	2	79/82

Table I references

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