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Sirolimus as a rescue therapy in children with immune thrombocytopenia refractory to mycophenolate mofetil

To the Editor:

Immune thrombocytopenia (ITP) represents the most common bleeding disorder in children characterized by the immune-mediated destructionof platelets and their precursorssecondary toproliferation and differentiation of autoreactive B-cells due to an abnormal T-cell response. Most cases in children have a self-limited course; however, the disease can become persistent or chronic.[1] The standard first-line treatment are steroids/intravenous immunoglobulins usually given with platelets count $<$20–30 $\times$ 10^9/L or in patients with significant bleeding symptoms regardless of platelet count.[1] Second/further-line therapies include splenectomy, rituximab, thrombopoietin receptor agonists, and immunosuppressant drugs; however, the choice is often individualized and based on the clinician's experience or guidelines[2] due to the lack of validated data. Mycophenolate mofetil (MMF) was shown to be effective in patients with ITP; however, some patients do not respond, especially those with primary ITP.[3]

Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor that has been showed to be effective in patients with autoimmune lymphoproliferative syndrome (ALPS) and other primary or secondary autoimmune cytopenias.[4] A prospective multi-institutional trial suggested that sirolimus was effective and safe in refractory cytopenias[5]; however, little data were reported on patients with primary ITP.

Herein, we report the results of a retrospective data review performed on ITP patients treated with sirolimus at the IRCCS Istituto Giannina Gaslini, Genoa (16 patients), and at University of Catania (3 patients). We included children with primary ITP or ITP secondary to an ALPS-related syndrome (ARS), which was defined as the presence of cytopenia and at least one absolute or primary additional criterion for ALPS.[6] Patients with definitive/probable ALPS[6] and with multilineage cytopenias were excluded.

According to the ITP International Working Group criteria,[1] responses to sirolimus were classified as a complete response (CR), which was defined as a platelet count $\geq$100 $\times$ 10^9/L; a partial response (PR), which was defined as a platelet count $\geq$30 $\times$ 10^9/L and at least a 2-fold increase from the baseline count; or no response, which was defined as a platelet count $<$30 $\times$ 10^9/L or less than a 2-fold increase from the baseline. Recurrence was defined by a platelet count $<$30 $\times$ 10^9/L or by the appearance of bleeding symptoms after sirolimus withdrawal in responding patients. Sirolimus was given at an initial dose of 2-2.5 mg/m^2/day. Serum levels were monitored to keep drug levels at 5–15 ng/mL. The response and toxicity were assessed by periodical clinical/biochemical follow-up.

Between 2005 and 2016, 19 patients (9 males, 10 females) with primary ITP ($n = 10$) or ITP secondary to ARS ($n = 9$) were treated with sirolimus. Median age was 9.8 years (range: 1.8–20), and 17 of the 19 (89%) patients had previously failed MMF treatment. The median time between diagnosis and sirolimus therapy was 22 months (range: 6–106). Thirteen patients (68%) achieved a response that was complete and partial in 10 (53%) and 3 (16%). Of the 17 patients who had previously failed MMF therapy, 11 (65%) responded to sirolimus rescue. The median time between starting sirolimus and achieving a PR or CR was 50 days (range: 14–135) and 158 days (range: 14–579), respectively. The patient's clinical characteristics, previous treatments, response, and toxicity are reported in Table 1. Five/Ten patients (50%) and 8/9 (89%) with primary ITP and with ARS-ITP, responded to the treatment, respectively ($P = 0.06$). One patient with ARS relapsed during tapering but recovered after dose adjustment. Sirolimus was given for a median of 15 months (range: 1–71). The median follow-up time was 21 months (range: 4–71). Treatment was well tolerated, and no adverse effects were reported.

To the best of our knowledge, this is the largest cohort of ITP patients treated with sirolimus, and the results show that the drug is safe and efficacious. Patients were treated with the same homogeneous approach and most were had previously received MMF. In previous reports, this drug given to adults and children with ITP was successful in about 50%-60% of patients[3]; however, the patients who did not respond required further-line therapies. In this study, most of the children who responded (85%) had previously failed to respond to MMF treatment demonstrating that sirolimus is an efficient rescue agent in these setting of patients. In addition, the treatment sequence of MMF followed by sirolimus, successfully used in ALPS patients,[7] can also be applied in patients with primary or secondary ITP.

Sirolimus is a mTOR inhibitor that targets the PI3K/AKT/mTOR pathway thus modulating B- and T-lymphocyte proliferation and, more specifically, abnormal T-cells. Contrary to MMF, it also promotes the proliferation of regulatory T-cells. Little data are available on the use of sirolimus in ITP. The only prospective study for autoimmune multilineage cytopenias[5] also included adults and patients with ALPS and thus showed very limited data for children with primary ITP. The largest cohort of children with ITP reported so far included 12 patients and showed that sirolimus was a safe steroid-sparing agent.[8] However, these patients were previously treated with different drugs, and sirolimus was mostly coadministered with steroids. In our homogeneous

TABLE 1 Clinical characteristics, previous treatments, response of each patient (A), and outcome of primary and secondary ITP (B)

A

Patient	ALPS-like signs	Line of treatment	Previous treatments[a]	Response	Number of days to PR/CR	Relapse	Toxicity
1	No	3	MMF	CR	—/43	No	No
2	No	3	MMF	NR		No	No
3	No	3	MMF	NR		No	No
4	No	3	MMF	CR	—/108	No	No
5	No	4	MMF, Eltrombopag	NR		No	No
6	No	3	MMF	CR	40/306	No	No
7	No	2	None	CR	—/14	No	No
8	No	3	MMF	CR	135/196	No	No
9	No	3	MMF	NR		No	No
10	No	4	Idroxiclorochine, MMF	NR		No	No
11	DNT, Ab	2	MMF	CR	—/120	No	No
12	DNT,LP	1[b]	None	PR	29/—	No	No
13	DNT,FAS	3	MMF	PR	37/—	No	No
14	DNT,Ab	3	MMF	CR	—/120	No	No
15	DNT	3	MMF	CR	103/ 579	No	No
16	DNT, LP	3	MMF	CR	88/239	No	No
17	DNT, LP, Ab	2	MMF	PR	27/—	No	No
18	DNT, Ab	3	MMF	NR		No	No
19	DNT	4	Rituximab, MMF	CR	60/425	Yes	No

B

	OR	CR	PR	NR
Primary ITP (n = 10)	5 (50%)	5(50%)	0(0%)	5(50%)
ARS-ITP (n = 9)	8(89%)	5(56%)	3(33%)	1 (11%)
Total (n = 19)	13 (68%)	10(53%)	3(16%)	6(32%)

[a]Other than steroids or immunoglobulins.
[b]This patient was treated with sirolimus as first-line therapy.
ARS, autoimmune lymphoproliferative syndrome -related syndrome; CR, complete response; DNT, double-negative T-cells; FAS, FAS-mediated apoptosis test positive; ITP, immune thrombocytopenia; LP, lymphoproliferation; MMF,mycophenolate mofetil; NR, no response; PR, partial response; OR, overall response.

cohort, sirolimus was introduced after steroid withdrawal or tapering and most patients were previously treated with MMF.

Almost 90% of children with ARS responded, suggesting that an underlying immune-dysregulation defect involving the mTOR signaling pathway could be present in these patients; however, three patients from this group were studied with a Next-Generation Sequence panel for immune monogenic defects with no results. Although there was no statistical difference with the overall response (OR) of patients with primary ITP (50%), a trend for an enhanced response in patients with other signs of immune-dysregulation, already reported when using MMF,[3,4] has also been shown in our patients. This highlights the need for an early and deep investigation of the immunity in patients with autoimmune cytopenias for a more targeted use of immunosuppressive drugs as second/further-line therapies.

In conclusion, this analysis shows that sirolimus represents a safe and useful agent in patients with primary or secondary ITP (other than ALPS) who fail MMF treatment, although further prospective studies are needed to confirm these results.

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AUTHOR CONTRIBUTIONS

MM*designed the research, cared for patients, and wrote the article.

GAR* performed the research, analyzed data, and wrote the article.

MG performed the research and analyzed data.

EP performed the statistic and cared for patients.

FF, FP,AP, CM, MC, RM, ML contributed essential data and cared for the patients.

GR and CD contributed essential data, cared for the patients and revised the manuscript.

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