LETTER TO THE EDITOR

Pidotimod in children with infectious mononucleosis: a preliminary randomized controlled study

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To the Editor,

Epstein-Barr virus (EBV) infection in adolescence and early adulthood may lead to infectious mononucleosis (IM) in 35-50% of the cases (1). The symptoms of IM typically subside in 1 to 2 months, even though a chronic disease may persist.

In many IM patients, the initial infection weakens the immune system by promoting subsequent secondary bacterial and viral infections (2). Therefore, secondary infections are possible during the acute phase of IM and include severe conditions, such as pneumonia and pericarditis.

From an immunopathological point of view, it has been reported that EBV infection interferes with transcription factors involved in immune response, promoting EBNA2 production that may allow secondary infections. Moreover, reactivation of the EBV is also possible: once IM (first infection) has been cured, it is never really eliminated from the body and may remain confined within the B lymphocytes in a state of quiescence. However, various pathogenic mechanisms, including stress, immunosuppressive treatment, and intercurrent viral diseases, may lower the immune function that induces a second IM infection (reactivation). Therefore, to increase immune response could be an intriguing new perspective in IM management. In this regard, pidotimod is a systemic thymic dipeptide that exerts an immunomodulatory activity (2). There is evidence that pidotimod causes maturation of dendritic cells, increases antigen presentation and toll-like receptors (TLR) 2 and 4, and induces cytokines of the innate and adaptive immunity affecting metabolomics (3). Based on this background, a recent study explored the clinical effect of pidotimod as adjuvant therapy in children suffering from IM (4). Children treated with pidotimod experienced shorter fever clearance time and hospitalization duration than controls. Moreover, pidotimod induced a significant reduction in the percentages of $CD3^+$ and $CD8^+$ T cells and an increase in the $CD4^+$ T cells and $CD4^+/CD8^+$ ratio. The current study was performed to investigate the effects of pidotimod concerning the resolution time and possible secondary infections in children and adolescents with IM.

MATERIALS AND METHODS

Forty patients, aged between 7 and 16, with symptomatic IM, were enrolled. The IM diagnosis was performed considering the clinical features and positive immunological tests. The 40 patients were randomly subdivided into two groups: group A

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included 25 patients (15 males and 10 females - aged between 7 and 16 years); group B included 15 patients (7 males and 8 females) between 9 and 15 years. The random list was based on blocks of 5 consecutive patients with a 5:3 ratio. The parents of the patients signed informed consent for participation in the study, and the Ethics Committee approved the procedure.

Group A was treated with pidotimod, administered on an empty stomach once a day, from the day of diagnosis and 30 consecutive days. The daily dose was 400 mg in patients between 7 and 12 years (10 patients) and 800 mg in patients between 12 and 16 years (15 patients). At the end of the first course, there was a 15-day suspension. Successively, a 10-day/monthly course was performed for six months. Group B (15 patients) was considered as a control arm and treated only with as-needed medications.

All patients underwent clinical monitoring at the end of the first month (T0), after four months (T1) and seven months (T2). The patients' parents had a clinical diary to record symptoms and medications. The primary outcome was the resolution time of IM, categorized if it occurred before the 14th day after the diagnosis or after. Secondary outcomes were the number of secondary infections.

The statistical analysis was performed using the χ^2 test.

RESULTS

Recovery time

At T0, at the end of the first Pidotimod course, 22 (88%) subjects of Group A and 3 of Group B recovered before the 14th day; 3 (20%) of Group A and 12 of Group B recovered after the 14th day ($p<0.0001$) (Table I). Stratifying for age, 10 children (< 12 years) were in Group A and 12 in Group B; there were 15 adolescents in Group A and 3 in Group B. In Group A, 7 (70%) children recovered before the 14th day as well as all the 15 (100%) adolescents. In Group B, 2 (16.7%) children recovered before the 14th day, and only one (33.3%) adolescent. The intergroup difference was significant in both groups: $p=0.0113$ in children and $p=0.0008$ in adolescents.

Reinfections

In Group A, only two (8%) subjects had reinfections, whereas 12 (80%) subjects of Group B had reinfections ($p<0.0001$), as reported in Table II. At T1, there were 16 infectious episodes in Group B:

Table I. *Recovery time in subjects with infectious mononucleosis and treated with pidotimod (Group A) and controls (Group B).*

	Group A (n.25)		Group B (n.15)	
	children ≤ 12 years	adolescents > 12 years	children ≤ 12 years	adolescents > 12 years
Resolution time ≤ 14 days	7 **(70.0%)**	15 **(100.0%)**	2 **(16.7%)**	1 **(33.3%)**
Resolution time > 14 days	3 **(30.0%)**	--	10 **(83.3%)**	2 **(66.7%)**
	n. 10	n. 15	n. 12	n.3

Table II. *Reinfections in subjects with infectious mononucleosis and treated with pidotimod (Group A) and controls (Group B).*

	Patients with ≥ 1 reinfection	Patients without reinfection
Group A (n.25)	2 **(8.0 %)**	23 **(92.0%)**
Group B (n.15)	12 **(80.0%)**	3 **(20.0%)**
χ^2 Test	P<0.0001	

10 infections were treated with acetaminophen and 6 with antibiotics. At T2, there were two infections in Group A treated with antibiotics, and four infections in Group B: 2 treated with acetaminophen and 2 with antibiotics. In Group A, the recovery time of reinfections was within the third day in one subject and the fifth day in the second subject. In Group B, the recovery time was within the third day in 2 subjects, Within the fourth day in six subjects, within the fifth day in 7; within the sixth day in 2; and within the seventh day in 3.

All subjects in Group A tolerated pidotimod, and no clinically relevant adverse event was reported.

DISCUSSION

The current preliminary study showed a shortening of IM resolution time: about 90% of pidotimod-treated achieved the complete recovery by two weeks, whereas about only 20% of controls recovered within that time. The other relevant outcome was the significant prevention of secondary infections: more than 90% of pidotimod-treated subjects did not experience any infection during the study, whereas 80% of controls had at least one infectious episode. Also, the resolution time of the secondary infections was remarkably shorter in the active group.

These results are consistent with the findings obtained in previous studies and confirm the immunomodulatory activity of pidotimod (5). In particular, pidotimod potentiated the beneficial effect of immunization of the influenza vaccine, possibly resulting in a more substantial activity of innate and adaptive immunity (6). *In vivo* studies showed a beneficial pidotimod effect on children, reducing the number of RI, the number of fever days, and the severity of signs and symptoms of acute infections (7, 8). A further clinical study reported that pidotimod improved the respiratory ciliary epithelium in children with RRI (9).

The current preliminary study had some limitations, including the open design, the limited number of participants, and the lack of objective parameters, even though it was designed as randomized and controlled. However, other studies should be conducted to confirm these preliminary findings.

In conclusion, the present study evidenced that pidotimod was able to shorten the recovery time, prevent secondary infections, and abbreviate their duration in children and adolescents with infectious mononucleosis.

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