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Investigations on the immunosuppressive activity of derivatives of mycophenolic acid in immature dendritic cells

Dorota Iwaszkiewicz-Grzes [a,b], Grzegorz Cholewinski [a,*], Agata Kot-Wasik [c], Piotr Trzonkowski [b], Krystyna Dzierzbicka [a]

[a] Department of Organic Chemistry, Gdansk University of Technology, ul. G. Narutowicza 11/12, 80-233 Gdansk, Poland
[b] Department of Clinical Immunology and Transplantology, Medical University of Gdansk, ul. Debinki 7, 80-211 Gdansk, Poland
[c] Department of Analytical Chemistry, Gdansk University of Technology, ul. G. Narutowicza 11/12, 80-233 Gdansk, Poland

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ABSTRACT

The main activity of mycophenolic acid **1** (MPA) and its analogs is the inhibition of proliferation of T cells. Here, we hypothesized that MPA and its conjugates inhibits also the activity of antigen-presenting cells (APC) including dendritic cells (DCs). We tested the effect of novel amino acid derivatives of MPA and conjugates of MPA with acridines/acridones on DCs by flow cytometry, ELISA and MLR assay. Both acridines/acridone derivatives could inhibit the maturation of DC, as shown by the decreased expression of B7 family receptors. It was confirmed in the mixed leucocyte reaction (MLR), in which T cells challenged with DCs pretreated with the analogs showed decreased proliferation and reduced cytokine secretion. The most interesting activity in this series of studies, that is, the suppression of CD86 receptor expression, decreased cytokine production and suppressed mixed leucocyte reaction, exhibited (mycophenoyl-*N*-3-propyl)-9-acridone-4-carboxamide ester **5a** and (mycophenoyl-*N*-5-pentyl)-9-acridone-4-carboxamide ester **5b**. These compounds reduced also the secretion of IL-2 and IL-15. In addition, they increased secretion of suppressive IL-10. Equally promising results were obtained for the *N*-mycophenoyl-D-glutamic acid **4b**, which previously gave the highest value of selectivity. Acridone derivatives of MPA are therefore good immunosuppressive drug candidates for further testing.

1. Introduction

The first successful renal transplantation was performed between identical twins and therefore there was no need for immunosuppression [1]. Since that time solid organ transplantation has been rapidly evolving as a life-saving therapeutic intervention that greatly contributes to a better quality of life in organ recipients. Genetic donor-recipient match is still the best guarantee of uneventful post-transplant follow up while appropriate immunosuppression is the most common strategy to keep the transplanted organ in good condition [2]. Unfortunately allograft rejection is still a major cause of graft loss in the first year posttransplant [3].

The inhibition of lymphocyte proliferation is one of the best maneuvers used in immunosuppression therapies. Mycophenolic acid (MPA) **1** is an uncompetitive inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH), the crucial enzyme in *de novo* purine nucleotide biosynthesis. There are two clinically approved derivatives of mycophenolic acid **1** (MPA, Fig. 1) – mycophenolate mofetil **2** (2-morpholinoethyl, MMF, CellCept (Roche), Fig. 1) and mycophenolate sodium **3** (MPS, Myfortic (Novartis), Fig. 1). MMF **2** is a prodrug metabolised to active form (MPA **1**) and first was used in early 1990s as an immunosuppressive drug. Both compounds, MMF **2** and MPS **3**, are used in the prevention of allograft rejection and treatment of autoimmune diseases [3–8].

The main activity of MPA and its analogs is the inhibition of proliferation of T cells, which stops these cells from allograft rejection [9]. Nevertheless, there are some reports suggesting that the drug inhibits also the activity of antigen-presenting cells (APC) [10]. It may be a special importance in transplantation as alloantigens presented by antigen-presenting cells (APC) trigger T cell alloresponse and graft rejection. The most important APC in the induction of such an immune response are dendritic cells (DCs), notably myeloid subset of DC (moDC), which are mainly considered as involved in organ rejection [11,12]. If it is true, MPA might be an agent that not only stops the proliferation of allosensitized lymphocytes, but also inhibits the allosensitization itself. Some changes to the particle structure might further enhance the latter activity without deteriorating the former one.

Hence, there were designed MPA immunosuppressive derivatives combining antiproliferative and anti-antigen-presentation activities, including amino acids derivatives of MPA and acridone/acridine analogs of MPA [13,14]. We evaluated their cytotoxic (IC_{50} - half maximal inhibitory concentration) in colorimetric test MTT (3-(4,5-dimethylthiazol-

* Corresponding author.
E-mail address: grzchole@pg.gda.pl (G. Cholewinski).

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