

The controversial early history of cyclosporin

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The biological effects of cyclosporin, namely immunosuppression and absence of cytotoxicity, were discovered in the course of a general screening program in which many scientists at Sandoz were involved. Contrary to some statements in the literature both Dr J. Borel and Dr H. Stähelin markedly contributed to the discovery and characterisation of the biological profile of the drug. In its subsequent exploitation Borel played the leading role. The outstanding clinical importance and the extraordinary commercial success of cyclosporin explain the widespread interest in the history of its discovery and development. It is also understandable that the recollection of the events by the individuals involved in the early phases of this history is influenced by subjective impressions and interpretations, which do not always reflect the historical facts. It is the purpose of this report to record and interpret the facts as accurately and as completely as possible on the basis of the available records.¹

Introduction

The immunosuppressive drug cyclosporin was discovered in the 1970s in the laboratories of Sandoz in Basel and later successfully marketed by this firm. Controversial reports about the discovery of the unusual immunosuppressive profile of the drug have been published. In the scientific literature, J. F. Borel generally appears as the principal discoverer [1–10], but H. Stähelin has challenged this view on various occasions [11, 12]. The management of Novartis, which as successor to Sandoz distributes cyclosporin, has asked us to re-examine the history of the immunosuppressive drug and express our opinion on the role of its principle proponents. We accepted this task because the intro-

duction of cyclosporin led to one of the major breakthroughs in medicine, e.g. in organ transplantation, so that its history, especially its earlier part, is of general interest.

Our presentation, which concentrates on the discovery and early development phases within Sandoz, is based on relevant publications, on inspection of internal documents from Sandoz (minutes of meetings, reports etc. as far as still available), and patent documents. Finally, as a confirmatory element, peers and managers from the former Sandoz company not directly involved in biological work with the drug were consulted.

An analysis of the available records

Discovery phase

In the Sandoz company in Basel a screening system for antibiotics has existed since 1958. In 1966 on the basis of a proposal from Dr A. Cerletti and Dr M. Täschler, an immunology laboratory led by Dr S. Lazary was established within the Cell Pharmacology group of Dr H. Stähelin. The aims of this group included the search for an immunosuppressive agent without major cytotoxicity. For this purpose Lazary and Stähelin had developed a mouse test in which immunosuppressive activity (by a haemagglutinin test) and cytostatic activity (by inhibition of tumor growth) could be measured in the same animal after intraperitoneal (ip) administration of the test compound [1, 2, 11, 13]. In the late 1960s, this group discovered ovalicin, a

fungal metabolite with the desired activity spectrum, which was subsequently abandoned due to unexpected toxicity in man [11, 14, 15].

In 1970, on the initiative of Dr K. Saameli, a general screening programme² in which Stähelin's group participated came into operation [11]. Later that year, Dr Jean Borel joined Sandoz and took over the well-equipped immunology laboratory from Lazary, who was leaving the company. The haemagglutinin test was included in the various assays of immunosuppressive activity [1, 11]. In late 1971, a fungal extract (24-556) containing cyclosporin as its main component was submitted to the general screening programme. A sample was also sent to Stähelin's laboratory for testing of potential immunosuppressive and cytostatic activity,

¹ We gratefully acknowledge the full cooperation of the Novartis organisation, which generously made the relevant documents available to us and supported our endeavour in every possible way.

² i.e. a programme in which compounds of synthetic or natural origin are routinely submitted to a battery of biological tests in order to detect activities useful for application in medicine.

using the above mentioned methods [1, 11]. The test for cytostatic activity was performed in Stähelin's personal laboratory using mice and a dosage schedule modified³ earlier by Borel. The haemagglutinin test, however, was performed in Borel's laboratory using the serum of the same animals [15]. Considerable immunosuppressive activity in the absence of major cytostatic activity was the observed outcome [1, 11, 16].

Shortly thereafter, a new batch of 24-556 was submitted directly to Borel's laboratory by the coordinator of the general screening programme. This time, no effect was seen in the haemagglutinin assay in mice treated with the new batch. It is not clear whether the same or a different galenical form⁴ as in the first experiment was used [17]. A slight immunosuppressive effect was however seen after oral administration [1]. In view of the strikingly positive results in the first experiment, research on the immunosuppressive potential of 24-556 was continued in spite of the disappointing findings in the second experiment.

Preclinical development

In preclinical development pure cyclosporin (27-400) was used. It was isolated in the Sandoz laboratories, its chemical structure was determined [18] and it was eventually synthesised [19]. The biological investigations (general pharmacology, pharmacokinetics, toxicology etc.) were performed in specialized units of Sandoz. Borel carried the main responsibility for the characterisation of the immunological properties of cyclosporin. He could, however, base his work on methods previously used by Lazary and Stähelin [1, 11]. In these experiments, the immunosuppressive effect of cyclosporin was confirmed in various experimental models, including skin and bone marrow transplantation studies in mice [17, 20].

The first publications on the biological profile of cyclosporin appeared in 1976, with Borel as the first and Stähelin as the last author [20, 21]. The preclinical and clinical research was complicated by the poor water solubility of cyclosporin and the

resulting galenical difficulties. Scientists within Sandoz, including Borel and Stähelin, contributed to the solution of this problem. Borel and Stähelin even participated as volunteers in a comparative study of the influence of various galenical forms on the bioavailability of cyclosporin organized by the medical department of Sandoz [22]. In this context a method for the determination of cyclosporin blood levels to which both Borel and Stähelin contributed was developed [1, 2, 11].

In spite of occasional setbacks, the preclinical development of cyclosporin was relatively straightforward. It took only four years from the discovery of the immunological effects to the green light for clinical testing. This indicates the interest of the research organisation in the drug, even though the sales estimates in 1976 were only 25 million Swiss francs for 1989 [23].

Clinical development

In April 1976 Borel gave a lecture at the spring meeting of the British Society for Immunology in London that was of major significance for the clinical development of cyclosporin. This lecture, which was based on the findings of Borel, Feurer, Gubler and Stähelin [20, 21], stimulated the interest of many scientists and clinicians, in particular the groups of Calne and White in Cambridge, U.K. [24-26] and Allison in London [27]. They subsequently started transplantation experiments with cyclosporin in animals and, impressed by the dramatic results, then applied cyclosporin to patients with kidney grafts. Additionally, Powles et al. carried out investigations with the drug in patients undergoing bone marrow transplantation. The impressive results from these groups were published in the *Lancet* in December 1978 [28, 29]. These communications were of great significance for the development of cyclosporin in transplantation medicine. Parallel to these efforts, extensive clinical investigations were initiated and managed by Sandoz. A description of these efforts is, however, beyond the scope of this communication.

Discussion

The *discovery* of cyclosporin occurred in the course of a general screening programme, which included a large team of scientists, including microbiologists, chemists, biologists, and pharmacologists. The decision by the research management of Sandoz to include testing for immunosuppression in this screening programme was an important precondition for the compound's subsequent discovery. The detection of the interesting biological profile of cyclosporin (immunosuppression without cytotoxic activity) occurred in the very first experiment carried out in the cell pharmacology group of Sandoz. Both Borel and Stähelin contributed towards this crucial experiment. Stähelin

and collaborators (especially Lazary) provided the experimental system aimed at detecting an immunosuppressant agent without major cytotoxicity and they also introduced the method (haemagglutination) that made the discovery possible. Furthermore the first experiments on animals were performed in Stähelin's laboratory, and it was in this laboratory that the clinically important absence of relevant cytotoxic activity was established. Borel's laboratory performed the haemagglutinin test, which demonstrated the immunosuppressive activity of cyclosporin. His modification of the application schedule may also have contributed to the positive outcome of the experiment. Thus, in our

³ Application of 24-556 on days 0, 1, 2, 3 instead of on days 1, 4, 7 after immunisation (Int. Document Sandoz 28.10.1970)

⁴ The publications of Borel and Stähelin [1, 2, 9] indicate two different formulations, which is not in accordance with internal Sandoz documents [15].

opinion, based on the available documented evidence, both Borel and Stähelin played instrumental roles in the discovery⁵ of the biological effects of cyclosporin, the contribution of Stähelin being at least equally as relevant as that of Borel. However, as the discovery was made in the course of an established screening programme with clearly defined aims, earlier inputs from other scientists were also important.

During the *preclinical development*, Borel efficiently provided the necessary data that together with the results from other units (toxicology, drug metabolism, galenics etc.) formed the basis for the initiation of a clinical trials programme. Borel also established and maintained important contacts to outside investigators who at an early stage realized the importance of the potentially unique contribution of cyclosporin to the development of transplantation medicine. The preclinical development phase proceeded rapidly whereby Borel had the support of his superiors in the research and development department. We conclude that a multidisciplinary team of scientists was involved in the preclinical development of cyclosporin. The immunological data were mainly provided by Borel and he also played a leading role in stimulating research on cyclosporin by outside investigators.

The fact that in the scientific literature Borel often appears as the sole or main discoverer of the immunosuppressant effect of cyclosporin [1–10] may be due to various reasons. Thus, Borel published and lectured extensively and he maintained numerous contacts with outside investigators, especially in the later phases of cyclosporin development in which Stähelin was less involved. Also, in some publications [2, 31] Borel did not quote the original seminal paper by Borel, Feurer, Gubler

and Stähelin [20]. Furthermore, Borel claimed incorrectly [32] that he himself had published “the first paper mentioning cyclosporin” in Immunology in 1976 [33]. In addition, Borel inferred that his persistence was important for the development of cyclosporin, since according to him, Sandoz had proposed to abandon the further development of the compound [1, 2]. We could find no evidence in the currently available Sandoz documents to substantiate this claim. In some publications with Borel as author or co-author, the personal engagement and continuous efforts of Borel in the research on cyclosporin are repeatedly emphasized whereas the role of others, especially of Stähelin, is less apparent [1, 2]. On the other hand, in a table in a joint publication of Borel and Stähelin [13], Borel is noted as the discoverer of the immunosuppressive effects of the cyclosporin-containing extract, 24–556. Later publications of Stähelin [11, 12] are in contrast to this statement. On the whole, the presentation of the early history of cyclosporin in the international literature was sometimes unbalanced and distorted and Borel’s role overemphasized [4–10].

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⁵ Neither Borel nor Stähelin appear as inventors on the cyclosporin patents [28]. This, in accordance with the legal requirements, is because the patents relate to cyclosporin as such.

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