A short history of anti-rheumatic therapy VIII. The immunosuppressants

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SUMMARY

The use of immunosuppressive drugs in rheumatology is fairly recent, having started just after the Second World War with the introduction of the first alkylating agents in oncohematology. When it became clear that some rheumatic diseases, particularly rheumatoid arthritis and systemic lupus erythematosus, show an immunomediated pathogenesis, with aspects of proliferation of the immunocompetent cells, immunosuppressive drugs soon found application in the treatment of such clinical disorders. This review outlines the historical milestones that led to the current use of drugs belonging to major groups of immunosuppressants, i.e., alkylating agents (cyclophosphamide), folic acid (methotrexate) and purine antagonists (azathioprine). Moreover, the history of cyclosporin A, the first immunosuppressant “selective” immunosuppressant agent and that of some immunoactive drugs recently used in rheumatology, such as mycophenolate mofetil, dapsone and thalidomide, is briefly described.

Key words: History of rheumatology, immunosuppressive drugs, cyclophosphamide, methotrexate, azathioprine, cyclosporin A, mycophenolate mofetil, thalidomide.

If pathological anatomy very much centered stage during the nineteenth century, with bacteriology gaining greater attention in the second half of that century, it was immunology, perhaps together with endocrinology, which most left its mark on the twentieth century. Although it had been conceived as a specialization in the last decades of the previous century, it is in the twentieth century, and above all from the 1950s onwards, that research in immunology has seen an expansion without precedent in the study of disease and therapies. It was obvious that this research would involve rheumatology and we could even say that this is the branch of medicine which has been most influenced by the advances in immunology. In fact, the interpretation of rheumatic diseases as being “allergic” was first proposed by Fritz Klinge (1), while the 1940s saw two discoveries which opened the way for immunological diagnosis of rheumatic diseases: that of the rheumatoid factor (2, 3) and that of the LE phenomenon (4). Immunoactive therapy had, however, already been started some time before, even though in the beginning it was used to respond to infection and, therefore, to boost the immune response and not suppress it. The anti-smallpox vaccine, introduced by Edward Jenner in 1796¹ and the anti-diptheria serum, introduced by Emil Adolf von Behring in 1892, can be considered two of the greatest achievements in medicine. (6) It was only in the 1940s the study began of drugs capable of depressing or suppressing the immune response. However, even in this case these drugs, at least in the beginning, were not intended so much

¹Inoculation of the smallpox vaccine which brings on a light episode of the disease and protects humans from a more virulent form, was already known in China and in the orient. Knowledge of it had been brought to England in 1721-22 by Lady Mary Wortley Montagu, who had seen it used in Turkey. Edward Jenner, a country doctor from Berkeley in Gloucestershire, came to the same conclusion. He had observed how farm laborers were generally immune to smallpox. In 1796, he confirmed his hypothesis by infecting an 8-year old boy, James Phipps, with human smallpox by injecting him with the liquid from a blister of a young milkmaid, Sarah Nelmes (5). This was in effect a smallpox vaccine and after an eight week incubation period, its efficacy was confirmed.
as a treatment of immune-mediated disease, but as a means of blocking cellular proliferation (from which we get the name cytostatic drugs) and, therefore, to be used in the treatment of neoplasms and malignant hemopathies.

However, very soon, in the mid-twentieth century, the first attempts were made to use these drugs as therapy for rheumatic disease. In 1947, in the United States, a team of dermatologists led by Earl D. Osborne (7), proposed the use of nitrogen mustard in the therapy of systemic lupus erythematosus (SLE). In 1951, Richard Gubner and his co-workers (8) proposed the use of aminopterin, and Carlos Jiménez-Díaz (9) proposed the use of nitrogen mustard in the treatment of rheumatoid arthritis (RA). The use of these drugs in the treatment of those rheumatic diseases in which there is a more obvious immunopathological mechanism, (in fact, at least in a historical context, SLE and RA) was justified by the fact in these diseases there is proliferation of a large number of immunocompetent cells (lymphocytes, plasma cells) and of cells involved in inflammatory response (macrophages) which can be reduced by cytostatic drugs. Only later, when the use of these drugs in diseases with an immune pathogenesis became more widespread, were immunodepressants or immunosuppressants added to the list of cytostatics (10).

First results were not of any particular interest. However, in spite of this, in the beginning there were many qualms about an extensive use of these drugs in the treatment of rheumatic diseases. In 1971, the ARA (American Rheumatism Association) formulated quite restrictive guidelines for their use in “non-neoplastic” diseases (11). There were two reasons for this. On the one hand, there was, at least initially, quite a high incidence of side-effects, some of which were serious. On the other hand, there were fears that an overall depression of the immune system could favour, as in fact these drugs do, infective complications or would re-trigger chronic infections which were clinically silent, above all tuberculosis, but there were also concerns about latent viruses such as herpes viruses.

Recent decades have seen a great change in the situation. The number of immunodepressants continues to grow and the problems related to their use have become ever more complex. Obviously, it is not within the scope of this review to analyze the enormous literature dealing with these drugs, and we excuse ourselves in advance with our readers for the inevitable omissions and imprecision. We will, therefore, limit ourselves to some historical background to the most important drugs which had or still have to play in the treatment of rheumatic diseases.

Let us look first at the story of the three historical “families” of immunodepressants: the alkylating agents (azoyprites), folic acid antagonists and purine antagonists. We will then examine the story of cyclosporin, which can be considered the first “selective” immunodepressant, and that of some of the more recent immunodepressants: mycophenolate mofetil and dapsone. We will finish by looking at the curious, or what has been called “schizophrenic” (12) drug, thalidomide.

Leflunomide also has the right to be considered as one of the group of immunodepressant drugs. However, here we will add nothing to what has already been written regarding its use in the treatment of rheumatoid arthritis given that, at least for the moment, it has only been used in the treatment of this particular disease (13). It is important to remember that even cortisones, at least at high doses, depress the immune system, and that many of the heterogeneous class of molecules which modify the aggressiveness of RA and improve the disease course (gold salts, chinolinics, thiols) interfere in some way with the immune mechanisms even though none of them can be considered immunodepressants in the strictest sense.

1) From a historical point of view, the first group of cytostatic immunodepressants to become available was made up of alkylation agents or azoyprites or nitrogen mustard. The term “alkylating agents” was derived from the fact that their action at a molecular level consists in substitution of
a H⁺ ion with an alkylic group (\(\text{C}_n\text{H}_{2n+1}\))

that of azoyprites from their chemical relationship with yprite, while the term mustard refers to its smell. The story of this group, in fact, begins with the “mustard sulphurs” which was synthesized in 1854. Contact with these sulphurs leads to the formation of characteristic blisters which had first been observed in 1887 (14). During the First World War, one of these substances, which had been synthesized by Victor Moyer in 1886 (15) and then called “yprite”, after the Belgian town of Ypres where the German army used it for the first time, was used to provoke skin, eyes and respiratory system lesions and this gave rise to the popular term “poison gas” which it became known under. In 1919, Edward Bell Krumbhaar (16) observed that intoxication by sulphur mustards was associated with leukopenia, bone marrow aplasia, and ulceration of the gastroenteric tract. In 1929, Isaac Berenblum (17) (Figure 1) confirmed that yprite also had an antineoplastic action.

In the years between the two world wars, many of the great powers continued, albeit with a certain discretion, studies into what became known as “chemical weapons” and alongside sulphur mustards were added the derivants of beta-chloroethylamine, the so-called “nitrogen mustard” or azoyprites, given their similarity to yprite. In the USA, responsibility for the study of the biological effects of azoyprites was given to Louis S. Goodman and Alfred Gilman, authors of a pharmacology treatise which is still widely read today and which has been translated into many languages. Together with Frederick S. Philips and other collaborators, they documented the marked cytostatic action on lymphatic and myeloid tissue (18). This suggested their possible efficacy in neoplasms of lymphatic tissue, such that in December 1942, at Yale, the first case of lymphoma was treated (19). Following this, other sources (20) mistakenly associated the discovery of the cytotoxic action of azoyprites to an event during the armed conflict at the end of 1943 in the port of Bari. During the bombing, a US merchant ship was sunk. On board there was a tank of azoyprites, ready to respond to a possible chemical attack on the part of the German army. Hundreds were intoxicated and 11 people died. In fact, postmortem examination confirmed a marked depression of lymphatic and myeloid tissue. The misunderstanding was favoured by the fact that the war was still on, and these investigations were, therefore, carried out in great secrecy since these agents were under strict military control. In fact, it was only at the end of the war that the research on these drugs entered the public domain. The first paper reporting this research was published in 1946 (21), after which the use of nitrogen mustard in the treatment of hematologic disease became more widespread.

As we have already seen, a nitrogen mustard, mecloretamin, was used experimentally in SLE in 1947 (7), in rheumatoid arthritis in 1951 (9), and later in other connective tissue and vascular diseases. Attempts were made to obtain a compound with less general toxicity using a prodrug (22), and this led, in 1958, to the synthesis of cyclophosphamide in the laboratories of the Asta Werke AG, thanks to the work of Herbert Arnold, Friedrich Bourseaux and Norbert Brock (23). Cyclophosphamide
has always been widely used in the treatment of an evergrowing number of rheumatic diseases\(^1\), above all in rheumatoid arthritis (25) and in SLE (26). It has also been used in Wegener’s granulomatosis and has radically changed the prognosis of this (27) and other connective tissue and vascular diseases. Cyclophosphamide can be administered either orally or by intravenous (iv) injection. But a particular method of administration, that of “pulse therapy” involving high individual doses administered by iv injection (28) was proposed at the end of the 1970s\(^4\) (29). This has the advantage of greater and quicker efficacy and a better tolerability than administration of small daily doses. In contrast, chlorambucil has been used less. Chlorambucil is less toxic but also has a less powerful action than cyclophosphamide. It was synthesized in 1953 (30) and mostly used in France.

2) While nitrogen mustard has a relatively long history, that of the folic acid antagonists is concentrated in just over a decade. In 1931, Lucy Wills (31) observed that megaloblastic anemia, that in India hit pregnant women, responded to a factor present in raw extracts (but not in purified extracts) of liver and in a yeast extract, Marmite®. This was, therefore, different to the extrinsic factor (which is simply vitamin B\(_{12}\)) the lack of which was responsible for the pernicious anemia (32). Folic acid (chemically known as pteroil glutamic acid) was so called because it is present in large quantities in the leaves of many green vegetables, above all spinach. It was, however, only identified by Herschel K. Mitchell, Esmond E. Snell and Roger J. Williams (33) in 1941. In the years immediately before, other factors had already been identified, such as folic acid: an active principle present in yeast and the liver needed for the growth of *Streptococcus faecalis*, isolated by Albert G. Hogan and Ernest E. Parrot in 1939 (34); LC factor, a growth factor for *Lactobacillus casei*, isolated in the liver and reported by Snell and by William Harold Peterson in 1940 (35); vitamin M, which can cure anemia in monkeys with pellagra, described by the team of Paul L. Day, again in 1940 (36). In 1945, Robert B. Angier, together with a series of collaborators (37), completed the synthesis of folic acid and, in the same year, the team of Tom Douglas Spies (38) used it in the treatment of pernicious anemia and of other megaloblastic anemias. Finally, in 1950, in the laboratory of William Shive (39), folinic acid, the active form of folic acid, was synthesized.

The observation that therapy with folic acid can favour tumor growth, in that it is essential for the synthesis of purines, which are basic constituents of nucleic acids, suggests that its antagonists could exert a cytostatic action. The first folic acid antagonist, aminopterin, was synthesized in the laboratory of the Calco Chemical Division (Cyanamid) thanks to research carried out by Doris R. Seeger (40) back in 1947. This molecule behaves like an inhibitor of dihydrofolato reductase, the enzyme which catalyzes the reduction of folate and dihydropholate to tetrahydropholate, that is into a biologically active form. The following year, the team of Sidney Farber (41) (Figure 2) of the Harvard Medical School in Boston, presented his first results, sensational for the time, on the treatment of acute leukemia in children with aminopterin. Given that, at that time, leukemia was considered incurable and it was believed that these children had to be left to die in peace, Farber’s results were received with mistrust and disbelief.

Shortly after, in 1951, antiopholics began to be used in rheumatology. In fact, in that same year, the team of Richard Gubner used aminopterin in the treatment of RA (8). As seen above, the use of immunodepressants in the treatment of rheumatic diseases caused some perplexity, even though the folic acid antagonists had already been used in the treatment of other diseases such as SLE, poli-dermatomyositis and psoriatic arthritis in the 1950s (42, 43). Two things

\(^*\)In 1959, it was shown that cyclophosphamide has a capacity equal to that of radiotherapy to inhibit the production of antibodies (24). Given this, cyclophosphamide was used, and is still widely used today, in the treatment of many immune-mediated rheumatic diseases characterized by the presence of antibodies.

\(^\#\)The efficacy, in terms of immunosuppressive potential, of intravenous bolus cyclophosphamide had already been shown in experimental murine models (29).
were needed before this group of drugs met a wider use. The first was the availability of a better tolerated folic acid antagonist, such as methotrexate (initially called ametopterin), which had already been synthesized in 1948 (44), and which was only used in clinical practice ten years later (45). The first paper reporting its use in RA was published 1962 (46). The second was the demonstration in 1972 by Rex T. Hoffmeister (47) that in rheumatic diseases this drug is active at lower doses than those required for use in hematologic diseases and with a single weekly administration, such that the question was raised as to whether, at these doses, methotrexate was effectively behaving as an immunodepressant or simply as an anti-inflammatory drug (48).

However, it was only some years later, at the beginning of the 1980s, that the ‘boom’ of methotrexate really took off (49), when it was realized that in this disease the “progressive” symbolic therapeutic approach, the “therapeutic pyramid” (50), had to be replaced by a more “aggressive” approach that popularly became known as “remodeling the pyramid” (51). This has meant that methotrexate is now not only first choice therapy for RA (52), but that use of this administration method has been extended to the treatment of numerous other inflammatory rheumatisms and systemic connective tissue diseases.

3) The third “historical” group of immunodepressant drugs is that of the purine antagonists (purine and folic acid antagonists are often considered together under the name of “antimetabolites”). As we know, the purine bases are essential constituents of nucleic acids for which it could be expected that drugs capable of impeding their synthesis and availability could have an antiproliferative, and consequently antineoplastic, effect. With this objective, in 1942, George H. Hitchings and Gertrude Belle Elion (Figure 3) started to investigate the problem in the laboratories of the Wellcome (53). Two of the first compounds, 8-azaguanine (54) and 2,6-diaminopurine (55), showed themselves to be efficacious in experimental tumors, but clinical results were disappointing.

The first concrete results arrived in 1952, when Elion (56) proposed 6-mercaptopurine which as a chemical compound had been synthesized, obviously without any investigation into possible therapeutic applications, by Hermann Emil Fischer as long ago as 1898. This proved itself to be efficacious in the treatment of leukemias and in particular of acute leukemias. But more than its antiproliferative action, 6-mercaptopurine...
topurine showed itself to be of interest for its immunodepressive action, such that the following years saw it being used in the treatment of SLE (57), of RA and other connective tissue diseases (58). In 1961, substitution with an imidazole ring of the hydrogen atom of the sulphhydryl group of 6-mercaptopurine led to the preparation of azathioprine (59). This rapidly became the drug of choice of this group because of its greater action and better tolerability, such that it was introduced very quickly into the treatment of SLE and RA (60). In reality, the inclusion of the imidazole group was not aimed at finding a more active compound but rather to find a compound with a longer action given that it was thought that it could protect the sulphphydrylic radical by a rapid methylation and oxidation, which could have rendered it inactive.

The story of the purine antagonists and the parallel story of the pyrimidine antagonists is, however, a good example of how research, if carried forward with determination, can lead to important results also in fields very different from those in which the research objectives were conceived. In fact, Hitchings and Elion discovered other drugs which have been widely used. Blocking the synthesis of nucleic acids, for example, can not only inhibit the proliferation of animal cells, but also that of pathogens of microorganisms. This concept led to the synthesis of an anti-malarian drug, pyrimethamine, back in 1952 (61), of an antibacterial, trimethoprim, in 1962 (62), of an antiviral, acyclovir, in 1977 (63), of an inhibitor of HIV replication, azidothymidine in 1985 (64). The 6-mercaptopurine is an analogus of hypoxanthine, as is allopurinol, an inhibitor of xanthine oxidase, which was synthesized in 1963 by the same group of researchers (65) and which is still considered a key drug in the treatment of hyperuricemia. Such a prestigious career could not fail to be crowned by a Nobel prize for medicine which was, in fact, awarded to Hitchings and Elion in 1988 (66).

4) At the beginning of the 1970s, the situation was, we could say, at a standstill. The three historical groups (the alkylating agents, the folic acid antagonists and the purine antagonists) had produced three drugs: cyclophosphamide, methotrexate and azathioprine, which still represent today the basis of immunodepressive therapy. All of these drugs are, however, what we would call “global” immunodepressants, in the sense that they are capable of inhibiting the proliferation of numerous cell lines. These involve practically all those with a rapid turnover, such as neoplastic cells, blood cells, but also, for example, those of the intestinal mucosa. This means that sometimes serious side effects are difficult to avoid, such as hematologic cytopenias and a greater susceptibility to infections. The search began, therefore, for more selective immunodepressants, that is, for drugs capable of inhibiting one or only a few cell lines, more directly involved in immune response. However, before selective immunodepressants were ready for use, selective cytostatic drugs had already been available for some time. These are drugs capable of inhibiting to varying degrees the proliferation of only one blood cell line, such as busulfan, a selective cytostatic drug which targets the granulocytic cell line which was introduced by Alexander Had- dow and Geoffrey M. Timmis (67) in 1953, and stilbamidine, selective sytostatic which targets the plasmocytic line, introduced by Isidor Snapper (68) as long ago as 1946.

Among immunodepressants, the first example of a selective drug could be considered to be cyclosporin. This drug has a very particular story (69, 70) and is, to a certain extent, controversial (71, 72). Cyclosporin is produced by a micromycete, *Tolypocladium inflatum* (Figure 4), which was found in Norwegian territory and isolated by Berthold Thiele in 1970 in the laboratories of Sandoz. In fact, for some time, the Sandoz employees had been invited some time before to collect soil samples during their work trips and holidays as part of the systematic search for potential antibiotics of fungal origin. The isolation of this newspecies of fungi was isolated precisely while analyzing one of these samples. Cyclosporin is a cyclic endeca-peptide which contains a non-conventional aminoacid (N-methylated). For this reason
it is not attacked by digestive juices and can, therefore, be administered orally. During the course of pharmacological investigations, which went on for some years, it was thought at first, in fact, to develop cyclosporin as an antibiotic antimycotic. In 1976, Jean François Borel (73) reported its ability to inhibit some immune responses and in particular to determine transplant rejection in humans, and cyclosporin was first used in 1979 as an anti-rejection drug. (74) Until then, prevention of transplant rejection was based on the use of high doses of cortisone and of azathioprine, and it was the use of cyclosporin that has been a determining factor in the great progress made in transplantation over the last decades. Subsequent research showed that cyclosporin specifically targets the CD4+ lymphocyte (75) which has a pivotal role in the immunopathological mechanism of RA for which it was proposed as basic therapy (76) and for those of other rheumatological autoimmune diseases, such as Behçet’s syndrome (77) and other non-autoimmune diseases, such as psoriasis (78).

The number of immunoactive drugs has increased considerably over recent years. But, as we have seen, we will limit ourselves to taking a look at just some of them. The story of mycophenolate mofetil began long ago. In fact, the mycophenolic acid was isolated in 1898 by the Italian Bartolomeo Gosio (79), from some liquid culture which contained Penicillium fungi and showed some weak antibacterial action. But this research did not lead anywhere and is of rather more interest in the story of antibiotics rather than that of immunodepressants. It was only in the 1960s that some researchers showed that this substance inhibited IMP-dehydrogenase and had an antiproliferative effect on some neoplastic cells (80). Some years later, experiments were carried out using the drug in the treatment of psoriasis (81). None of these investigations, however, proved successful due to the high incidence of undesirable gastrointestinal side effects. These were not seen when, in 1982, a prodrug of mycophenolic acid was synthesized: mycophenolate mofetil (82). This was then used both as an anti-rejection drug, and in the treatment of various immune-mediated diseases, such as, for example, dermatomyositis (83) and Takayasu’s disease (84).

The story of dapsone also began long ago. This sulfone was synthesized in Germany in 1908, even though there was no interest in any possible therapeutic application until 1932, when the German Gerhardt Domagk discovered the antibacterial action of sulfones and of sulfonamide (85). Dapsone was introduced in India at the end of the Second World War by the Englishman Robert Greenhill Cochrane to treat leprosy (86). It proved itself to be the first drug to show efficacy in this disease.
was subsequently used in the therapy of some dermatoses, in particular those bullous dermatoses characterized by infiltration of granulocytes and neutrophils, from which comes the influx at the lesion level. However, the drug interferes with immune mechanisms and has efficacy, albeit modest, in experimental arthritis. Its use in the treatment of rheumatic disease, introduced in various contexts in the 1970s and 1980s, is not particularly widespread, above all for the incidence of undesirable side effects, some which are quite serious, such as metemoglobinemia, even though its efficacy in bullous SLE eruptions has been confirmed (87), and in particular in recurrent polychondritis (88).

The story of thalidomide is an interesting one not so much for its role in the treatment of rheumatic diseases, which is on the whole quite marginal, but for the strange circumstances of its use. It was synthesized in 1954 by a small German pharmaceutical company, Chemie Grünenthal, and was put on the market in 1957 as a sedative-hypnotic drug (Figure 5). But after only a few years, in 1961, it was condemned because, if administered to women in pregnancy it caused serious fetal malformation and in particular, phocomelia, that is the incomplete formation of the limbs (89, 90). The huge controversy which followed from this, obviously led to the drug being immediately taken off the market. But is also led to bitter controversy about the excessive ease with which certain drugs were put on sale without their complete safety being documented. Besides which, since then, international regulatory agencies have stipulated that for all new drugs, toxicological tests must include tests to exclude teratogenicity. However, in 1964, a French doctor, Jacob Sheskin, although he knew about the controversy surrounding thalidomide, administered the drug to a patient with erythema nodosum leprosum, an extremely painful complication of leprosy which makes it impossible to sleep. There was a dramatic improvement in the patient’s clinical condition and this was later confirmed in other cases (91). It was then discovered that thalidomide reduces the high levels of TNFα (92) and inhibits neoangiogenesis (93). It was then, obviously with due caution, used with great success in patients with RA who were refractory to other therapies, (94), discoid and subacute SLE (95), Behçet’s syndrome (96) and, occasionally, in other rheumatic diseases (97).

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