A risk of infection on the decline

The risk of infection is increased by the simultaneous or sequential use of multiple immunosuppressive therapies. The prescribed dosage is also a significant factor. For example, the mortality risk due to infectious diseases in patients on steroid therapy is doubled but this is not observed with azathioprine and methotrexate used alone. The TNF inhibitors (e.g. infliximab, etanercept), widely prescribed today, appear to be associated with only a very small increase in certain infections.

In the last few years, the increased risk of infection associated with immunosuppressant therapy has significantly decreased because of exhaustive initial investigation, remedial or prophylactic anti-infectious measures and strict clinical and biological surveillance.

An increased multifactorial cancer risk

The oldest immunosuppressant agents (such as cyclophosphamide) have a confirmed carcinogenic potential. Non-specific inhibition of the immune system alters the body’s capacity to detect and destroy cancerous cells. The cancers most frequently encountered in immunocompromised patients are often those linked to the activation of a specific virus (e.g. Human Papilloma Virus or Epstein-Barr virus).

In organ transplant recipients, the incidence of new cancers is 3 times that of the general population but about half of these cancers are not very aggressive and are relatively easily treated, for example skin cancers. In renal transplantation, some cancers seem to be related more to the kidney disease than to the immunosuppressant treatment itself. Other factors, such as immunosuppression prior to transplantation, the intensity and duration of immunosuppressant therapy, age, tobacco consumption and, above all, heredity may explain the increased risk of cancer.

The risk of cancer is much lower in auto-immune disease with the possible exception of patients receiving high cumulative doses of cyclophosphamide.

It is interesting to note that some of the latest generation of immunosuppressants (e.g. sirolimus, everolimus) seem to have many side effects, in particular an increased incidence of infections and certain cancers. Modern immunosuppressants, such as sirolimus, which target a specific inactivation of the immune or inflammatory mediators or signalling pathway in the immune or inflammatory response in a more specific manner, have helped to improve therapeutic results in addition to reducing side effects, particularly with regards to infection and cancer. Additionally, as we have already seen, clinical experience of managing immunosuppressant therapy is increasing with time and today we are better able to prevent, detect and treat the major side effects of this type of therapy.

Today’s immunosuppressants

The last decades have seen the development of immunosuppressant therapies for many diseases. The first powerful but non-specific agents used (corticosteroids, azathioprine, etc.) had many side effects, in particular an increased risk of infections and certain cancers. Modern immunosuppressants, such as sirolimus, which target a specific modulation or signalling pathway in the immune or inflammatory response in a more specific manner, have helped to improve therapeutic results in addition to reducing side effects, particularly with regards to infection and cancer. Additionally, as we have already seen, clinical experience of managing immunosuppressant therapy is increasing with time and today we are better able to prevent, detect and treat the major side effects of this type of therapy.

Cardiovascular risk is difficult to assess

Although it is recognised that steroids are associated with the development of the metabolic syndrome, that ciclosporin and sirolimus can adversely affect the lipid profile and that tacrolimus may induce diabetes, the impact of these adverse metabolic effects on patient survival and cardiovascular morbidity has still to be demonstrated. The potential cardiovascular risks of immunosuppressant therapy should not obscure the concrete risks posed in this context by chronic renal disease before and after transplantation.

Under these circumstances it is difficult to determine the precise contribution of immunosuppressants to increased cardiovascular risk.

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It is interesting to note that some of the latest generation of immunosuppressants (e.g. sirolimus, everolimus) seem to possess their own inherent tumour prevention properties. This seems promising for the future.

However, these patients are usually closely monitored by medical professionals and their tumours tend to be diagnosed at an early stage, allowing effective therapy with better survival.
HIV infection: 1996 — a new story begins

The revolution in antiretroviral therapy

The first therapies using a combination of antiretroviral drugs were introduced in 1996. These are commonly referred to as “triple therapies” or HAART (Highly Active Antiretroviral Therapy).

Change in the number of AIDS-related deaths in France 1994 to 2006.

These therapeutic protocols result in a rapid rise in CD4 levels and in a significant reduction of the viral load, even when prescribed at a late stage for patients already with AIDS. In the long term, daily lifelong treatment allows the immune system to recover, which explains the astonishing reduction in AIDS-related morbidity and mortality since the year 2000. There has been no fall-off in the efficacy of the antiretroviral treatments which has remained stable over time.

Viral load and CD4 count over time in an untreated HIV infected patient

New data, new hope

HIV infection has inspired a research effort unparalleled in the history of medicine giving rise to a considerable degree of optimism.

Therapeutic strategies targeting the body’s immune response

The principal complications of untreated infection with HIV include the development of AIDS and cancers attributable to immunodeficiency. These are fatal in 99.9% of cases.

The efficacy of antiretroviral therapies has controlled the problem of immunodeficiency but led to a series of clinical problems that are considered “co-morbidities”.

We now know that the activation of the immune system and the inflammation caused by the replication of the virus itself promote long-term co-morbidity, in particular cardiovascular, bone, cerebral and malignant diseases. This emphasises the need to monitor the patients’ immune response.

HIV-related co-morbidities

Since the year 2000, our understanding of HIV-related co-morbidities has improved. For example, the increased cardiovascular risk is seen as being due not to the antiretroviral drugs but to the viral infection itself. Similarly, the observed increased risk of cancer in HIV positive patients is not related to AIDS itself but to other risk factors superimposed on the HIV infection, for example smoking (lung cancer) or co-infection with Hepatitis B or C (liver cancer).

Are these treatments effective in the long term?

A 2009 French study (1) evaluated the benefits of ten years of antiretroviral therapy. In patients treated at very late stages of HIV infection, the CD4 count reached about 200 and, after ten years, it continues to rise. However, permanent recovery of the immune system depends on an important factor, patient compliance — i.e. adherence to treatment and the ability to take antiretroviral medication on a daily basis.

Anti-HIV vaccine and eradication of the virus — from dream to reality

The first successful clinical trial of an anti-HIV vaccine was carried out in Thailand and published in 2009 (2). It showed that infection was prevented in 31.2% of those vaccinated. Although the efficacy of this vaccine is still too limited, these results are very promising and the research continues.

In addition, the first case of a (permanent?) cure was reported from Germany, also in 2009 (3). A patient suffering from leukaemia received a bone marrow transplant from a donor with a genetic deficiency affecting theCCR5, the virus receptor molecule, the patient currently has an undetectable viral load. This development has given rise to new optimism that this unique experience can be reproduced.

Triple therapy improves the life expectancy of HIV infected patients, most noticeably when the CD4 lymphocyte count exceeds 500/mm³ and viral load remains below the detectable threshold.

Sources


New physiopathological concepts

Immunosuppressive therapy: its infectious and oncological complications

• Autoimmune diseases are the result of an aberrant activation of the immune system resulting in the non-recognition of the body’s own tissues and a self-destructive reaction.
• After organ transplantation the immune system may also cause harm through the destruction and rejection of the transplanted organ.

These are two examples for which the preferred treatment is the use of drugs that reduce the immune system’s response “immunosuppressants”.

The immune system carries out essential infection and tumour inhibiting functions which explains why patients undergoing therapy reduce immunodeficiency are particularly susceptible to infections and are at increased risk of developing cancer.

Are we correct to consider the current life expectancy of an HIV-positive patient undergoing treatment and whose immunity has been restored to as 30 to 35 years?

*An early study referred to a life expectancy of 29 years. Life expectancy is constantly being recalculated because of the therapeutic progress achieved in countries where treatment is widely accessible. Nevertheless, a longer follow-up is needed to evaluate this development, particularly since algorithms will inevitably facilitate the calculation of life expectancy. We believe that the co-morbidities of atherosclerosis and cancer are caused mainly by the HIV infection and not by the therapy. This is the current consensus. We are therefore moving in the direction of very early treatment because this would prevent the development of atherosclerosis and cancer if we succeed, we have every reason to believe that patients should have normal life expectancy, even if we are unable to eliminate all reservoirs of the virus.

Professor BRIGITTE AUTRAN

Immunosuppression

Cancer

Anti-HIV vaccine and eradication of the virus

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