Fundamentals of Treatment for Autoimmune Diseases

Seiji MINOTA

Professor and Chief, Division of Rheumatology and Clinical Immunology, Jichi Medical School

Abstract: Autoimmune diseases are dichotomized into organ-specific and systemic one. Hashimoto’s disease, Addison’s disease, and pernicious anemia are the representatives of the former and systemic lupus erythematosus of the latter. Systemic disease is treated mainly by rheumatologists and organ-specific disease is in the hands of the specialists to the organs involved. Autoantigens specific to the organs involved are targeted in organ-specific disease, and, nuclei without organ-specificity are the main targets in systemic disease. Although more concrete evidence of autoimmune phenomena for their pathogenesis is obtained in organ-specific disease than systemic disease, immunosuppression by glucocorticoids and immunosuppressants is applied only to the latter. It is very difficult to determine the amount of glucocorticoids least but sufficient to suppress the disease, and, it is sometimes based upon the doctors’ experience. This is why it is called “art instead of science” how to use glucocorticoids. On the other hand, hormone replacement therapy is the treatment-rule for organ-specific disease instead of immunosuppression and it might be even forgotten that autoimmune process underlies there. These two categories of autoimmune disease are in striking contrast in terms of both pathogenesis and treatment.

Key words: Systemic autoimmune disease; Organ-specific autoimmune disease; Glucocorticoid; Immunosuppressive agent; Pernicious anemia

Introduction

Autoimmune diseases are roughly divided into two categories: systemic and organ-specific. The former is a group of diseases, which is called collagen-vascular diseases more popularly. Organ-specific autoimmune disease is the one usually not in hands of rheumatologists but in those of the specialists for the organs involved, such as endocrinologists, neurologists, gastroenterologists, and so on.

There are two interesting features between the...
two groups. First, organ-specific autoimmune diseases have more concrete evidence for the involvement of autoimmune processes than systemic ones, such as the evidence for existence of autoantigen-specific T lymphocytes. Secondly, in spite of this, immunosuppression by glucocorticoids or immunosuppressive agents is applied to only systemic autoimmune diseases and almost never to organ-specific ones. As a matter of fact, it is sometimes forgotten that organ-specific autoimmune diseases have autoimmune mechanisms underlain for the pathogenesis.

These aspects are easier to understand when we review the characteristics of the two groups of autoimmune diseases.

**Characteristics of Systemic Autoimmune Diseases**

**Organ-Nonspecific Autoimmune Diseases, So-Called Collagen Vascular Diseases**

Let's look at the disease character of systemic lupus erythematosus (SLE) as a representative of systemic autoimmune diseases. It is well-known that patients with SLE have antinuclear antibodies in their circulation as the most paramount feature. Every nucleated cell in the body has a nucleus inside, and there is no organ-specificity in this regard. Anti-nuclear antibodies interact with nuclei and elicit inflammation by consuming complements when nucleated cells are destroyed and release the nuclear materials in the circulation or in the tissue fluids.

Kidney is the organ targeted most frequently in SLE and the resultant glomerulonephritis is called “lupus nephritis”. Sixty to seventy percent of the patients with SLE develop lupus nephritis, although autoantibodies strictly specific to glomeruli are scarcely seen. As mentioned above, lupus nephritis develops as a result of immune complexes formed in the circulation or in situ, which eventually accumulate in glomeruli.

There are three major anatomical characteristics of the kidney in this regard. First, kidneys receive ~25% of the blood that is pumped up by the heart every minute. That is, they receive ~50 times more blood than other organs in the body based upon weight by weight. Therefore, the kidney is an organ quite rich in blood flow. Second, glomerular vascular structure is composed of afferent arterioles, glomerular capillaries, and efferent arterioles. As a matter of fact, glomerular capillaries are sandwiched by the arterioles. Probably due to this anatomical characteristic, pressure in the glomerular capillary is ~4 times higher than the one in the capillaries elsewhere. Thirdly, the kidney is an apparatus for filtering body fluid and it makes ~150l/day of glomerular filtration. Immune complexes could passively be deposited in the glomeruli from patients with SLE as a result of these anatomical and physiological characteristics.

There are many reports indicating that anti-dsDNA antibodies, in particular, have strong glomerulonephritogenic activities. Thus, treatment modality has been developed to eliminate B cells specific for anti-dsDNA antibodies, although it is not widely prevailed. A part of anti-dsDNA antibodies might indeed more preferentially be deposited in the glomeruli than autoantibodies specific for other autoantigens, it is quite difficult to ascribe lupus nephritis to only one autoantigen-autoantibody system. Because anti-dsDNA antibodies are highly specific to SLE and reflect the disease activities in most cases, lots of autoantibodies, in terms of both quality and quantity, specific to many cell components are produced by the time anti-dsDNA antibodies emerge and, consequently, higher amount of immune complexes are deposited in the glomeruli.

Because T lymphocytes are indispensable for antigen-specific antibody formation, it is widely believed that they play a pivotal role also in autoantibody production in SLE. However, one of the most perplexing things in systemic autoimmune diseases is the difficulty in show-
ing the existence of such T lymphocytes in SLE.2) We are only speculating indirectly the presence of such T lymphocytes by analyzing the molecular characteristics of autoantibodies including anti-nuclear antibodies.3) Questions remain to be answered as to autoantigen which initiates the autoimmune process.

Fundamentals for the Treatment of Systemic Autoimmune Diseases

Because of the reasons mentioned above, it is impossible, at this moment, to utilize autoantigens or a part of an autoantigen to eliminate pathogenic and antigen-specific T or B lymphocytes. Therefore, overall immunosuppression is needed to achieve sizable effects in the treatment of systemic autoimmune diseases.

1. Glucocorticoids (Corticosteroids)

After all, glucocorticoids are most frequently used for the treatment of systemic autoimmune diseases. How to use glucocorticoids in treating autoimmune disease is largely based upon one’s experience and this is why it is called “art instead of science” to use glucocorticoids. They have both anti-inflammatory and immunosuppressive effects. For example, prednisolone less than 30 mg/day exerts mainly anti-inflammatory activity, while immunosuppressive effects seem to appear when it is used at the dose of more than 50 mg/day. Glucocorticoids show their effects by binding to the receptor located in the cytoplasm and, after migrating to the nucleus, the complexes bind to the specific sites of the glucocorticoid-responding genes with the resultant protein production.

However, anti-inflammatory effects would be brought about not by inducing glucocorticoid-inducible proteins but by the mechanisms that follow. Transcription factors such as AP-1 and NF-κB are required in order for cells to produce inflammation-inducing proteins that would be released into their microenvironment. The transcription factors accelerate enormously the transcription rate of the inflammatory proteins by binding to the upstream of those genes. Complex molecules composed of glucocorticoids and their receptors bind directly to AP-1 and NF-κB in the nucleus and block the latter molecules to bind their specific transcription sites, thereby inhibiting the production of inflammation-inducing proteins.

On the other hand, immunosuppressive effects of glucocorticoids would be due to the alteration qualitatively and quantitatively in the function of T lymphocytes and antigen presenting cells. Thus, prednisolone less than 30 mg/day is used when anti-inflammatory effects are pursued and more than 50—60 mg/day of prednisolone are needed to achieve immunosuppressive effects. There are big variations among artificial glucocorticoids in their half-lives when given in vivo, and we need to understand that the longer the half-lives, the more potent in both their beneficial and deleterious effects. Glucocorticoids show anti-inflammatory effects very swiftly, while immunosuppression is a late effect.

2. Immunosuppressive agents

A group of drugs classified as immunosuppressive agents is usually used as an adjunct to glucocorticoids instead of being used solely. They are slow-acting compared to glucocorticoids. Azathioprine and cyclophosphamide are more frequently used than cyclosporine A and FK506 in Japan. However, the latter two are required to suppress T-lymphocyte function more specifically. Cyclophosphamide is used either per os every day or intravenously as a pulse-therapy once a month. The latter is believed to be less toxic with almost equal beneficial effects.

Outline of Organ-Specific Autoimmune Diseases and Fundamentals of the Therapy Thereof

Organ-specific autoimmune diseases are dichotomized from the therapeutic point of view. Hashimoto disease, Addison disease, pernicious
anemia, and type I diabetes mellitus comprise one side and the other side includes multiple sclerosis for example.

Let’s look at the pernicious anemia caused by deficiencies of vitamin B\textsubscript{12} or folic acid. Vitamin B\textsubscript{12} needs to couple to the intrinsic factor, which is released from the parietal cell of the stomach, to be absorbed via the specific receptor located in the ileum. There are two kinds of autoantibody found in pernicious anemia: the one which inhibits the binding of vitamin B\textsubscript{12} to the intrinsic factor\textsuperscript{6} and the other which blocks the binding of vitamin B\textsubscript{12}-intrinsic factor complex to the receptor in ileum.\textsuperscript{7} Production of intrinsic factor is decreased in atrophic gastritis, where antibody- and cell-mediated autoimmune mechanisms are operative in destroying parietal cells in the stomach.

Although pernicious anemia is induced by an autoimmune mechanism, its specific therapy is intramuscular injection of vitamin B\textsubscript{12}. Glucocorticoids or immunosuppressants are never used to suppress the autoimmunity which underlies pernicious anemia. This principle holds true in Hashimoto’s disease, Addison’s disease, and type I diabetes mellitus. Replacement therapy with thyroid hormone and insulin is applied to Hashimoto’s disease and type I diabetes, respectively. Although glucocorticoids are indeed used for treatment of Addison’s disease, this is not for suppression of autoimmune mechanism but for the replacement of the adrenal hormone. Therefore, glucocorticoids in high amount are never used in Addison’s disease. Even if the function of these endocrine organs is destroyed completely through autoimmune mechanism, replacement therapy with the corresponding hormone is possible and much safer than aggressive immunosuppressive therapy.

The situation is quite different in multiple sclerosis and replacement therapy is not applicable here. Autoimmune process per se must be stopped to improve central nervous system function and we need to resort to glucocorticoids in high dose or immunosuppressants just like in systemic autoimmune diseases.

Number of autoantigens eliciting autoimmune process is fewer in organ-specific autoimmune diseases than in systemic autoimmune diseases and the identification of their molecular nature is rapidly progressing. We hope, in the near future, to suppress autoimmune process by the specific autoantigens or the epitopes thereof.

Conclusion

Most organ-specific autoimmune diseases are treated by endocrinologists and the replacement of hormone is the treatment principle. It is sometimes forgotten that autoimmune mechanisms are operative in these organ-specific autoimmune diseases.

On the other hand, many organs are involved in systemic autoimmune diseases and the introduction of high dose glucocorticoids or immunosuppressants is the treatment rule. Glucocorticoids also have adverse effects systemically and it is quite important to use the smallest amount required to suppress disease processes. However, this is very difficult to achieve and it is often referred to as “art rather than science” to decide the amount of glucocorticoids to be used. It might be a trick to start treatment with enough amount of glucocorticoids and to taper as swiftly as possible. We need to be alert to opportunistic infections around 4 weeks from the initiation of the treatment and prophylactic measures should be taken by checking and referring to the number of total lymphocytes or CD4$^+$ T lymphocytes.

REFERENCES

3) Sontheimer, R.D. and Gilliam, J.N.: DNA antibody class, subclass, and complement fixation in systemic lupus erythematosus with and


