"No Safe Dose in Glucocorticoids"

Eric Morand, M.D., Ph.D., Director of Rheumatology at Monash Health in Australia, speaks with Rheumatology Network about his recent article in Nature Reviews Rheumatology.

First used as a treatment for rheumatoid arthritis in 1949, glucocorticoids have become the most widely used treatment for inflammatory disorders. But recent research suggests that the well-known side effects of glucocorticoids may be more damaging than previously realized. A 2014 paper published in the journal *Rheumatology* for example, found that prednisone treatment worsened long-term damage, including osteoporotic fractures, cataracts and diabetes mellitus, in patients with systemic lupus erythematosus.

A new article published this month in *Nature Reviews Rheumatology* spotlights high healthcare costs for patients treated with glucocorticoids for lupus and also points to some promising research into alternatives. A study released this year in the journal *PNAS* found that the calcineurin inhibitor cyclosporin might combat glucocorticoid resistance by acting on resistant T<sub>H17</sub> cells. Even if cyclosporin proves an inappropriate treatment, the research reveals a biochemical pathway that researchers can target to combat glucocorticoid resistance, Monash University researchers Sarah A. Jones, Ph.D., and Eric P. Morand, M.D., Ph.D., wrote in *Nature Reviews Rheumatology*.

Another promising path points to glucocorticoid-induced leucine zipper protein, or GILZ. This protein had previously been found to protect against inflammation in multiple systems. Research published in 2015 found that this protection extends to inflammation related to psoriasis and systemic lupus erythematous. Meanwhile, Jones and Morand published work finding that GILZ regulates the proliferation and effector gene expression in T<sub>H17</sub> cells and B-cells, which may, in turn, keep inflammation in check.

*Rheumatology Network* spoke with Morand to discuss these major glucocorticoid findings of 2015, and to learn more about what research lies ahead.

1. What are the troubling side effects of glucocorticoids?

Morand, M.D.,Ph.D.

The side effects are the same as the effects of natural glucocorticoid hormones in the body. They include weight gain, raised blood pressure and blood sugar, infections, skin changes, acne, osteoporosis and heart disease. But new evidence suggests that the consequences of lupus itself may be made worse by glucocorticoid treatment, which creates a paradox as the acute inflammation of lupus is clearly treatable with these drugs.

2. What causes these side effects? Are drug interactions a problem with glucocorticoid treatment?

The metabolic side effects are easily understood as the effect of an amount of glucocorticoid above the natural requirements, as the natural hormone modulates these body systems in a desirable way in health. We still don’t really know how glucocorticoids can amplify the long-term harmful outcomes of lupus and so more research is needed, but there’s no direct evidence that it’s a drug interaction.

3. You summarize a paper that found high costs associated with glucocorticoid treatment. What is known about how much of that cost is related to pre-existing disease severity versus complications of these drugs? How could that research question be addressed in the future?

The health economics of glucocorticoids are still being worked out in lupus and it’s not clear how much of the cost relates to the pre-existing state of the individual patient. I think that formal health economic analysis of this question is needed; especially as potentially ‘steroid sparing’ new drugs may be unfairly compared to low-cost glucocorticoid pills unless the full cost of use is known.

4. Is there a way to ameliorate the side effects of glucocorticoids?

The best way to avoid the side effects of glucocorticoids is to reduce their use, as all the side effects — including the apparent worsening of the long term effects of lupus — are very clearly dose-dependent. The trouble is we do not have any other fast-acting broad-spectrum immune-suppressing drug currently available. I hope that biological therapies moving towards the market may give us these alternatives. It’s impossible to recommend any specific drugs such as cyclosporine without proper clinical trials, but the recent basic science findings are of high interest.

5. What about alternatives to glucocorticoids? Why is GILZ so promising?

There is a long history of searching for drugs that have the beneficial but not harmful effects of glucocorticoids, but so far this has not borne fruit. GILZ is naturally occurring protein which has immune-modifying effects and is switched on by glucocorticoids, suggesting it is an important natural player in the beneficial effects of glucocorticoids in lupus.

Recent findings from two separate groups indicating a powerful effect of this protein to control the development of B cells strengthens the idea that it could represent a key target in the search to find an alternative to...
glucocorticoids. Central to this is that so far no major metabolic effects of GILZ have been found.

6. What hurdles remain to turning GILZ into a feasible treatment?

The main hurdle is that this is an intracellular protein and delivering it requires either solving the problem of how to get the protein inside the cell (which we and others are working on) or identifying a molecular interaction that can be mimicked, for example with a small molecule compound.

7. For now, how should doctors weigh the risks and benefits of glucocorticoids when making treatment decisions?

For now, the best advice is to be mindful that there is no safe dose of glucocorticoids and to safely maximize the use of other therapies to enable the lowest possible dose of glucocorticoids to be used in every case.

References:


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