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Recognition of Glucocorticoid Toxicity and the Need for Alternative Treatments for Inflammatory Disease: An Expert's Opinion

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You're listening to *Living Rheum* on ReachMD. This medical industry feature, titled "Recognition of Glucocorticoid Toxicity and the Need for Alternative Treatments for Inflammatory Disease: An Expert's Opinion," is sponsored by Sanofi and Regeneron. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD and I'm your host Dr. Charles Turck. Today we'll be speaking with Dr. John Stone. He's an expert in spotting glucocorticoid toxicity and identifying the need for alternative treatments for inflammatory disease. Dr. Stone is a Professor of Medicine at Harvard Medical School and the Edward A. Fox Chair in Medicine at the Massachusetts General Hospital in Boston. John, thank you for being here.

Dr. Stone:
Thank you for having me, Charles.

Dr. Turck:
Let's begin with the current basics for clinical glucocorticoid use. What do they treat and how are they used?

Dr. Stone:
Glucocorticoids, or GCs, are mainstays of treatment for many diseases and are effective at treating many inflammatory conditions, especially in primary care. Examples of these conditions span many therapeutic areas, including dermatological, respiratory, rheumatic, and gastrointestinal diseases. In particular, atopic dermatitis, asthma, polymyalgia rheumatica, and inflammatory bowel disease are commonly treated with GCs in the clinic, and the judicious use of GCs in patients with those conditions often leads to meaningful improvements in symptoms. In some cases, the treatment course with GCs is brief, lasting only a week or two, for example, in the control of an asthma flare. In others, however, chronic GC therapy is needed for disease control.

The guidelines for best uses of GCs to treat conditions across these therapeutic areas always recommend trying to minimize the dosage and length of use. For example, the 2021 American College of Rheumatology Guidelines for rheumatoid arthritis recommend that GCs should be used at the lowest effective dose for the shortest duration possible. Despite these recommendations, chronic courses remain common for many patients and many diagnoses. It's not uncommon for GC use to last in some patients for many years. This can occur in patients with chronic or severe disease who are unable to get off GCs without a worsening of their condition.

Dr. Turck:
That's interesting to know. What are some of the effects that patients may see when they're treated with the GC for so long.

Dr. Stone:
Well, adverse events, or AEs, from GC treatment have been shown to be related both to the average dose and the cumulative duration of treatment. The risk of a GC-treated patient experiencing complications from these therapies only increases with treatment length. One recent study evaluated data from more than 2,000 patients across a variety of disease indications. The patients took an average of 16 milligrams of prednisolone equivalent. Up to 90% of the patients in that study experienced GC toxicity if the treatment exceeded 60 days.

GC toxicity may impact many different organ systems throughout the body, including psychological or behavioral side effects. There are also multiple ophthalmological, cardiovascular, or metabolic side effects with these treatments. Common adverse effects include mood

and sleep disturbances, glaucoma, cataracts, skin thinning or bruising, headaches and infections. In some cases, these treatment related AEs are severe, resulting in a permanent decline in overall health. For instance, the risk of developing diabetes, hip or osteoporotic fracture, and heart failure all increase with the use of GC therapy.

One particularly concerning statistic is that in one study, all-cause mortality increased more than sevenfold for patients who took as little as 7.5 milligrams of prednisolone equivalent per day. These data were reported in a comprehensive study of more than 150,000 patients over the age of 40 years. Part of this increased risk likely stems from patients' underlying disease, but GC toxicity probably also plays an important role since it may increase infections, cardiovascular morbidity, and overall frailty.

It's also been reported that 58% of patients who received commonly prescribed courses of GC's experienced two or more serious adverse events, not just one side effect at a time.

Dr. Turck:
Those statistics are sobering. You did mention that AEs from GC treatment can be dependent on dose and duration of treatment. Can you elaborate on what that might mean? Are some symptoms more likely at higher or lower doses?

Dr. Stone:
Yes, that is correct. The toxicity effects of GCs depend generally on both the dose and duration of treatment, but there are nuances to this statement when it comes to the specific details of individual toxicities. That is to say, the different AEs associated with GC use have variable relationships to the quantity and length of treatment. In fact, two broad patterns have been observed.

Clinicians refer to a linear path of GC toxicity, which should be distinguished from a threshold pattern. For AEs that follow a linear path, the incidence of the adverse effect increases continuously with increasing cumulative dose. Edema, skin thinning, a cushingoid body habitus, shortness of breath, and sleep disturbances fall into this category. Alternatively, though some other AEs are only observed once a certain threshold of GC dose has been reached. These adverse effects include glaucoma, cataracts, depression, and an increase in blood pressure.

Some threshold pattern adverse effects have a very low threshold dose, such as cataracts, which have been reported at doses of less than 5 milligrams of prednisolone per day. Other examples of adverse effects associated with the threshold pattern of toxicity also include avascular necrosis of joints and pathological fractures of bone.

Even when GC's are taken as recommended, adverse effects are still common. In my opinion, we have struggled to find the appropriate dose and/or duration of GCs that balance the benefits as opposed to the adverse effects for conditions in which chronic use is required. Although adverse effects are more common at higher doses and with chronic use, they are not limited to these cases. Even very low dose GC treatment can cause adverse events. For example, fractures as a result of GC treatment, both non vertebral and vertebral, may occur as soon as one month after GC treatment initiation with as little as 2.5 milligrams a day.

One study also showed that although the bone loss associated with 2.5 milligrams per day of prednisone was preventable, anti-osteoporosis medications used in clinical practice were unable to fully prevent bone loss in patients receiving doses of 5 milligrams a day or more.

It's clear that the fracture risk among patients who are being treated with GCs is heightened beyond what would be expected simply from changes in bone mineral density. Low doses of GCs have also been associated with increased risk of heart failure.

Many common AEs from GC toxicity have been reported in patients taking less than 5 milligrams of prednisolone per day. These include hospitalization for infection, depression, sleep disturbances, skin thinning, weight gain, increase in blood pressure, edema and cataracts, among many others. Patient susceptibilities to certain AE's clearly plays a role in how GC toxicities unfold.

Dr. Turck:
Does that mean there are certain risk factors that contribute to how susceptible a patient is for GC toxicity?

Dr. Stone:
Yes. The things I pay the most attention to are age, dose, and duration of GC therapy, patient medical history and other medications that the patient may be taking. Age is important in this setting. Elderly populations have higher rates of comorbidities that may be exacerbated by GC use. Dose and duration required for treatment is also a consideration because high doses may increase risk and may be required for some diseases or for more severe disease. Long duration of treatment increases risk and cumulative GC dose and exposure, which can occur when patients are unable to get off GC's without having an exacerbation of their underlying disease.

Third, I consider the patient's history of underlying comorbid conditions, including osteoporosis, diabetes mellitus, glaucoma, and uncontrolled hypertension, which are likely to be exacerbated by GC use. Finally, concomitant use of other medications may present

risk for toxicity because GCs are known to have interactions with other immunosuppressive drugs, with non-steroidal anti-inflammatory drugs, and with anticonvulsants.

Dr. Turck:
In cases when GC therapy is unavoidable, are there any steps that can be taken to mitigate a patient's risk of experiencing toxicity?

Dr. Stone:
There are two different sides of this, the healthcare provider perspective and, of course, the patient's perspective. Healthcare providers and patients must work together to optimize clinical outcomes in patients treated with GCs to reduce, as much as possible, the adverse effects associated with GC use. First, healthcare providers can use the tools at their disposal to obtain a baseline assessment of the patient's health and then routinely monitor for changes. A typical baseline assessment for patients starting GC therapy should include a physical examination, a comorbidity evaluation taking into consideration medical history, baseline laboratory tests, and a bone density test. Medical history is really important because the susceptibility to GC toxicity may be impacted by a patient's current and past dose, medications taken at the same time, and infection history. In addition, a patient's vaccination status is important because GC's may reduce vaccine efficacy.

A lateral spine X-ray may also be considered in adults older than the age of 65, or in children taking GC's for more than 3 months, to examine for vertebral fractures. Important blood tests to examine at the start of GC therapy include a hemoglobin A1C and lipid profile.

Dr. Turck:
And on the patient side?

Dr. Stone:
On the patient side, education about GC toxicity symptoms is important, this way they can be on the lookout for any new symptoms and know when it's important to inform their healthcare provider of any concerning changes. There are also a few positive lifestyle changes patients should consider that may lower their risk of GC toxicity. These include, weight bearing exercise, diet modifications and limiting smoking and alcohol intake. All of these factors are important to the early recognition and prevention of GC toxicity.

Dr. Turck:
What steps can be taken to help prevent or manage GC toxicity in cases when GC therapy is unavoidable? What role do disease specialists play?

Dr. Stone:
Specialists are an important resource for mitigating GC toxicity. In primary care, after disease diagnosis and the start of GC treatment, a standard treatment path would include symptom improvement and or remission, followed by GC tapering, and ultimately, discontinuation. Despite regular monitoring and prevention strategies, however, some patients remain at high risk for, or still experience, GC toxicity. These patients may have a more complex treatment progression or be unable to taper off GC successfully, and this is where the role of the disease specialist is particularly important. They can help patients navigate complicated situations and give recommendations on alternative treatments specific to their field. In addition, if a patient is in an at-risk population for GC toxicity, or suffers an adverse event from GC treatment, or can't discontinue GC's without having a flare of their underlying disease, referral to a disease specialist may be necessary to look for alternative treatments.

Dr. Turck:
Could you elaborate on the possibility of alternative treatment?

Dr. Stone:
Certainly. Over the last 20 years, many steroid-sparing options have become available as alternatives to GC's. These options differ depending on the patient's condition. Many of these new therapies have revolutionized treatment for inflammatory diseases. Alternative therapies to GC's are available in inflammatory conditions, such as inflammatory bowel disease, polymyalgia rheumatica, atopic dermatitis, and asthma. But the need for alternatives still exists in many other areas. There are also many more alternative therapies now in development being studied in clinical trials that may be available soon.

Dr. Turck:
It sounds very exciting and promising. Since we're about to wrap things up, John, could you give us a quick recap?

Dr. Stone:
Of course. GCs are successfully used to treat many different inflammatory diseases, but their use can be associated with the potential for toxicity, even at low doses. Patients on GC therapy should be monitored and educated about possible side effects. Ultimately, disease specialists should be utilized for more complex patient cases. They may recommend using steroid-sparing alternative

treatments to improve inflammatory disease symptoms while reducing the risk of GC toxicity.

Dr. Turck:
It was great to speak with you today. Thank you for your time.

Dr. Stone:
Thank you, Charles. I've enjoyed this.

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This medical industry feature was sponsored by Sanofi and Regeneron. To revisit any part of this discussion or to find others in this series, visit *Living Rheum* on ReachMD.com, where you can Be Part of the Knowledge.

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