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CHAPTER 5
Tocilizumab In Giant Cell Arteritis: Better Understanding The Benefits

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CHAPTER 5
Glucocorticoids have been the treatment mainstay for giant cell arteritis (GCA) for several decades (1). Current guidelines recommend glucocorticoids as an induction therapy, and they also clearly outline tapering schemes and options for flare management. Methotrexate can be used as a glucocorticoid-sparing strategy, but this approach is not supported by strong evidence (2–5). In 2017, the Tocilizumab in Giant Cell Arteritis (GiACTA) trial provided strong evidence for a good risk/benefit ratio of tocilizumab in GCA (6). Based on the results of GiACTA, which included 251 patients, the US Food and Drug Administration and the European Medicines Agency approved this drug for the treatment of GCA. Several recent and ongoing trials with biologics or JAK inhibitors (JAKi) offer even more promise of further optimizing GCA therapy. These developments include the use of mavrilimumab (an IgG4 humanized monoclonal antibody blocking the granulocyte–macrophage colony-stimulating factor receptor α), ustekinumab (an interleukin-12/23 inhibitor), and the JAKi baricitinib. A recently published proof-of-concept study demonstrated that baricitinib at 4 mg/day permitted discontinuation of glucocorticoids in most patients with relapsing GCA. Specifically, 13 of the 14 patients who completed 52 weeks not only achieved disease remission but also discontinued glucocorticoids (7).

Against this background arises the question of how to quantify the actual benefit of combining glucocorticoids with tocilizumab or possibly other biologics/JAKi. The GiACTA trial provided 2 obvious answers. First, clinical effectiveness is improved, i.e., sustained remission occurred in significantly more patients treated with subcutaneous tocilizumab as compared to those in the placebo group (P < 0.001 for the comparisons of either active treatment to placebo) (6). Second, glucocorticoids could be spared. The cumulative median prednisone dose over the 52-week period was 1,862 mg in each tocilizumab group (162 mg administered either weekly or every other week) as compared to 3,296 mg and 3,818 mg in both placebo groups (6). The favorable clinical effects achieved by reduction of the glucocorticoid dose, however, is currently only known in a very incomplete manner. Nevertheless, some publications recommend adjunctive therapy with tocilizumab as a first-line glucocorticoid-sparing agent for patients with a) new-onset GCA and increased risk for glucocorticoid-related adverse effects or complications, relapse, or prolonged therapy, or b) refractory or relapsing disease (3,5). Other recommendations, such as the recently published Pan American League of Associations for Rheumatology Guidelines, go even further and conditionally recommend that patients with newly diagnosed GCA receive treatment with glucocorticoids and tocilizumab over glucocorticoids alone (8). However, our assessment published in 2020 still stands, which states that it remains to be demonstrated which subgroups of GCA patients...
would benefit most from tocilizumab treatment in terms of reduced glucocorticoid toxicity, cost-effectiveness, and effect on treatment duration (3).

A study by Patel et al published in this issue of Arthritis & Rheumatology is beginning to close these gaps in our knowledge (9). For the first time, there is detailed information on the effects of prednisone and tocilizumab on hemoglobin A1c (HbA1c) levels during the treatment of GCA. These findings reveal very valuable insight into the complicated interplay of disease- and treatment specific factors as well as carbohydrate metabolism of patients with GCA. In fact, many aspects of the relationship between GCA, its treatments, and diabetes mellitus have been previously studied. In Figure 1A, we provide an overview of studies and describe identified influential factors regarding type 2 diabetes/glucose tolerance in GCA.

Patel and colleagues describe a strong relation between tocilizumab treatment and reduced HbA1c levels, which are independent of daily glucocorticoid dose (Figure 1B). In addition, they show a positive association between HbA1c levels and daily glucocorticoid dose. Therefore, this study is the first to provide new insights into the direct benefits of tocilizumab regarding HbA1c levels. Furthermore, in contrast to previous studies, which have suggested a rather low diabetes prevalence rate at the time of GCA diagnosis (10,11), Patel et al observed a higher number of prediabetic and diabetic patients upon study entry. Prior epidemiologic studies on risk factors for GCA development have demonstrated that higher glucose and HbA1c levels and a higher body mass index were protective against GCA development (10–13). Therefore, this new study by Patel and colleagues emphasizes the need for further investigation of these conflicting findings and the interrelation between inflammation, HbA1c levels, and diabetes in GCA patients in both observational and interventional studies.
Figure 1. The many facets of giant cell arteritis and carbohydrate metabolism. A, Evidence from studies on GCA regarding glucose tolerance or risk of type 2 diabetes mellitus. Numbers next to the arrows indicate the respective references. Arrow colors indicate the direction of influence, i.e., green arrows indicate a generally beneficial downstream influence with regard to the risk of glucose intolerance or type 2 diabetes, while red arrows indicate generally unfavorable effects. B, In the study by Patel et al (ref. 9), 72% of patients receiving glucocorticoids (GCs) alone and 77% of those receiving both GCs and tocilizumab (TCZ) had prediabetes or diabetes at baseline. After 52 weeks of follow-up, 64% in the glucocorticoid-only group and 33% in the tocilizumab/glucocorticoid group had prediabetes or diabetes. The categorization of HbA1c values was as follows: <5.7% normal, 5.7 to <6.5% prediabetes, ≥ 6.5% diabetes. GiACTA = Tocilizumab in Giant Cell Arteritis trial.
While this study undoubtedly provides novel and interesting findings, it also has 2
main limitations from our point of view. First, as is often the case with randomized
controlled trials, the generalizability of the trial results is limited. For example, patients
with chronic kidney disease (serum creatinine level of >1.4 mg/dl for women and >1.6
mg/dl for men) and patients who needed intravenous glucocorticoids were excluded
from the GiACTA trial. Moreover, only a very small fraction of patients was non-White.
Whether the results of the trial can be applied to patients not represented within is
difficult to know. Second, the comparator for tocilizumab in this trial was placebo.
Consequently, the effects of tocilizumab on HbA1c cannot be compared to other
glucocorticoid-sparing agents such as methotrexate, which, according to the EULAR
2018 guideline (5), could be used as an alternative to tocilizumab in patients
relapsing or in patients with a high risk of glucocorticoid-related adverse events.

GCA patients belong to a disease spectrum with differences in clinical picture,
systemic inflammation, and vessel involvement. GCA patients with high levels of
systemic inflammation have higher levels of plasma pyruvate kinase M2, a glycolytic
enzyme important for cellular glucose metabolism in GCA (14). This association
between systemic inflammation and cellular glucose metabolism supports the idea of
a link between disturbed glucose metabolism and inflammation in GCA. However,
there is no direct association of HbA1c and glucose levels with inflammatory markers
in GCA patients, suggesting that additional factors play an important role (15). This
is consistent with the study by Patel et al, in which tocilizumab seems to have a direct
effect on HbA1c levels in GCA. The question is whether patients with a higher
inflammatory burden will benefit more from tocilizumab than those with low levels of
inflammation, and whether the additional benefit of tocilizumab on HbA1c levels will
be the same in this group of patients. Whether drugs like methotrexate and the other
upcoming glucocorticoid-sparing treatment options including baricitinib have the
same effect on HbA1c levels remains to be investigated. It is important to mention
that despite the new treatment options, a large group of GCA patients continue to
receive high-dose and long-term glucocorticoids (64%, 40%, and 34% after 2, 5,
and 10 years following diagnosis, respectively) (16).

In the study by Patel et al, a high daily glucocorticoid dose was directly associated
with high HbA1c levels and the development of prediabetes and diabetes. These data
highlight that a fast and short glucocorticoid taper in GCA should be used to prevent
development of prediabetes and diabetes in GCA. Moreover, tocilizumab initiated
immediately following GCA diagnosis together with a rapid tapering of
glucocorticoids has additional value in normalizing HbA1c levels in GCA.
The research area discussed here is narrow, but it has great depth, which arises from the following question: What are the net clinical benefits of using a biologic treatment (which itself is not without adverse effects) to reduce the glucocorticoid dose needed? Of course, it is not enough to look only at HbA1c or carbohydrate metabolism in this regard. Rather, it will be necessary to also quantify effects on, e.g., blood pressure, bone health, lipid metabolism, infection risk, Cushingoid appearance, and the development of glaucoma and cataract. At the same time, full monitoring of the largest possible cohorts of patients with GCA treated with glucocorticoids and/or without tocilizumab should also include monitoring of residual inflammatory activity.

As erythrocyte sedimentations rate and C-reactive protein inflammatory markers no longer function reliably under treatment with tocilizumab, additional parameters such as thrombocytosis, anemia, and fibrinogen should be determined. Not only is this necessary to assess therapy success but also because increased inflammatory activity, per se, negatively influences glucose tolerance, metabolism, bone health, and infection risk. The breadth of the research question results from the degree to which the findings can be extrapolated. In the case of GCA, glucocorticoids naturally have a particularly dominant significance, but glucocorticoid-sparing is a key task in many other inflammatory rheumatic (and other) autoimmune diseases, as well (e.g., other vasculitides, systemic lupus erythematosus, myositis, and rheumatoid arthritis).

Of course, this also relates to the question that remains incompletely answered of what can really be achieved as a clinical benefit (i.e., the quantified reduction of glucocorticoid-induced side effects), considering all relevant influencing factors. Here, the study by Patel et al is exemplary, even though the focus is very narrow compared to the wide range of known glucocorticoid side effects.
References
