semaglutide and dulaglutide. Future studies should examine patient preferences in terms of the devices used as this preference might have implications in real life.

When choosing the next glucose lowering drug for patients with type 2 diabetes, health-care practitioners need to consider multiple factors in addition to glycaemic efficacy to personalise treatment approaches on the basis of individualised treatment targets. Such factors might include the effect on weight, hypoglycaemia, cardiovascular risk, diabetes-related complications, tolerability, ease of use, durability of effects, interactions with other drugs, a patient's age, and renal or hepatic impairment. Although two head-to-head trials of semaglutide versus other weekly GLP-1R agonists[9,10] have shown glycaemia and weight advantages with semaglutide, treatment decisions should allow for differences in trial designs and the generalisability of the findings in a real-life setting. For example, the SUSTAIN 7 findings apply to patients who were only on metformin and who were at relatively low cardiovascular risk since patients with renal impairment, established cardiovascular disease, and advanced diabetic retinopathy were excluded. Additionally, much more information as to the relative usefulness within the class of these drugs from real world settings is required to establish their true place in the management of type 2 diabetes.

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Graves' orbitopathy: the ongoing search for new treatment strategies

Graves' orbitopathy is an autoimmune process affecting the orbital tissues of patients with Graves' disease. The disorder generally occurs in patients with Graves' hyperthyroidism, or a history thereof, but can also occur in euthyroid patients without a history of thyroid disease or in hypothyroid patients with Hashimoto's thyroiditis.[1] Local inflammation leads to enlargement of the extraocular muscles and an increase in orbital fat, which can lead to proptosis, diplopia, eyelid swelling and retraction, and a feeling of pressure or pain. Graves' orbitopathy typically starts with an active progressive phase followed by a quiet, or inactive, phase. During the active phase, the goal of treatment is to minimise discomfort and prevent complications. In mild cases,

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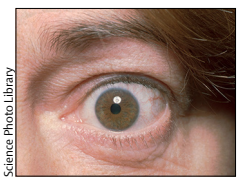
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treatment may be limited to local measures, control of risk factors (eg, smoking cessation), and 6 months treatment with selenium.[2] In moderate-to-severe cases of active disease, intravenous glucocorticoids (methylprednisolone) are considered the first-line treatment,[2] because they have higher efficacy and fewer side-effects than oral glucocorticoids.[3] Despite this evidence, oral steroids are still commonly prescribed in many countries.[4]

Although treatment with high-dose glucocorticoids shows acceptable outcomes in most patients, a substantial number of patients have disease progression despite treatment or experience relapse after treatment cessation. More effective treatment approaches are therefore still needed in Graves' orbitopathy. In a multicentre, randomised, placebo-controlled trial, impressive results were achieved with teprotumumab, a human monoclonal antibody inhibitor of the insulin-like growth factor-1 receptor, suggesting that this is a disease-modifying drug in Graves' orbitopathy.[5] However, this drug is not yet available in clinical practice and more data on its effects compared with intravenous methylprednisolone are needed to establish its role in the treatment of moderate-to-severe active Graves' orbitopathy. In two clinical trials[6,7] reported in *The Lancet Diabetes & Endocrinology*, two other easily available immune-modulating therapies were tested. The results of these trials are of great importance as they could have direct clinical implications.

In a randomised, observer-masked clinical trial done in 164 patients, George Kahaly and colleagues showed that 24 weeks of treatment with a relatively low dose of mycophenolate mofetil (720 mg per day) in addition to the current first-line treatment (intravenous methylprednisolone at 500 mg per week for 6 weeks, then 250 mg per week for 6 weeks) had improved efficacy versus intravenous methylprednisolone alone.[6] Although the trial's primary outcomes—response rate at 12 weeks and relapse rate at 24 and 36 weeks—were negative, after 24 weeks, treatment responses were seen in 53 (71%) of 75 patients who received the combined treatment compared with 38 (53%) of 72 patients who received intravenous methylprednisolone alone, and the effect was sustained to 36 weeks. Although treatment-related side-effects were slightly more common in patients receiving the combined treatment (39 events with the combination *vs* 29 events with monotherapy), no patients discontinued treatment or required a dose reduction because of drug-related toxic effects. Since mycophenolate mofetil is affordable and easily available in most countries, these data suggest that combination therapy with glucocorticoids and low-dose mycophenolate mofetil can be useful as first-line treatment for patients with moderate-to-severe active Graves' orbitopathy, although follow-up data from an observation period longer than 12 weeks after the cessation of mycophenolate mofetil treatment are needed to show a sustained effect.

Rathie Rajendam and colleagues studied the addition of azathioprine or radiotherapy to oral prednisolone using a 2×2 factorial, double-blind, randomised controlled trial.[7] Although some studies have suggested that radiotherapy potentiates the effect of oral glucocorticoids[8] and might be especially useful to improve restricted ocular motility,[9] its use is not widely accepted because of evidence questioning the benefits of radiotherapy for Graves' orbitopathy in general.[10] Current guidelines recommend orbital radiotherapy plus oral glucocorticoids as one of the treatment options when patients have partial or no response to intravenous glucocorticoids.[2] Importantly, Rajendam and colleagues' study shows no benefit from the addition of radiotherapy to oral prednisolone as first-line treatment for moderate-to-severe Graves' orbitopathy. Although it could be argued that oral prednisolone is no longer standard of care according to current guidelines, it is still widely used.[4] Furthermore, if radiotherapy adds little to clinical outcomes when combined with oral glucocorticoids, it is perhaps even less likely to be valuable when added to the more potent therapy (ie, intravenous glucocorticoids). The data regarding the benefits of the addition of azathioprine to oral steroids are more difficult to interpret. Although there was evidence to suggest a beneficial effect of azathioprine when it was added to oral prednisolone, a very high number of patients withdrew from treatment. Additionally, it is not clear whether the addition of azathioprine to the more potent intravenous glucocorticoids would have had similar effects. On the basis of the results of this study, neither radiotherapy nor azathioprine should be regarded as first-line treatment options in Graves' orbitopathy.

Both of these clinical trials[6,7] underline the need for further evaluation of novel treatment strategies for patients with Graves' orbitopathy. Various pathogenic

processes are involved in Graves' orbitopathy,[11] including inflammation, adipogenesis,and fibroblast activation. These processes could provide novel targets for therapy and are all subjects of ongoing research. Preclinical and clinical studies have investigated immunomodulatory drugs, including disease-modifying antirheumatic drugs and next-generation biologicals. Methotrexate, rituximab, and anti-tumour necrosis factor-α and anti-interleukin 6 therapies have all been the subject of clinical studies in Graves' orbitopathy, sometimes with conflicting results.[12] Additionally, direct targeting of orbital fibroblasts with tyrosine kinase inhibitors, including imatinib and dasatinib, was shown to be effective in in-vitro studies.[13]

The conflicting results in some clinical studies and the diversity of pathogenic processes that might play a part in each patient with Graves' orbitopathy mean that a personalised, patient-specific, pathway-targeting treatment is required that is tailored to the stage of disease to improve therapeutic efficacy. Identification of biomarkers, determination of cytokine profiles, or assessment of the therapeutic efficacy of various compounds targeting the pathways involved in pathogenesis using ex-vivo whole orbital tissue cultures could help to improve this personalised treatment approach and patient outcomes.

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Gout: a patrician malady no more

While historically thought of as a disease of aristocratic men (so-called patrician malady), gout, in the 21st century, continues to be an interesting challenge. Irrespective of the initial clinical presentation, the disease evolves as the patient ages and acquires comorbidities. The last three decades have been remarkable in terms of drug discovery through knowledge of the mechanistic[1,2] and genetic aspects of hyperuricaemia and gout.[3,4] The development of new classes of pharmaceutical agents, which are now available for acute and chronic gout therapy (eg, febuxostat, lesinurad, and pegloticase), has changed the field substantially. These changes have not only empowered physicians but also patients, who are finally beginning to understand the chronicity of this disease. Concurrently, there has been renewed interest in the repurposing of extant drugs used for other clinical indications (eg, colchicine, anakinra, canakinumab, losartan, and fenofibrate).

Complicating matters, however, are the various challenges in the appropriate management of chronic gout—health system factors and the practice setting in which the clinician is treating the patient. Huge disparities exist in practice patterns among health-care providers because of the insufficient understanding of gout as a chronic progressive disease and knowledge about available therapeutic choices. Gout does not go


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