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ABSTRACT

Glucocorticoids (GCs) are the gold standard for treatment of giant cell arteritis (GCA); however, there is a need for studies on GC-sparing agents, given that up to 85% of patients receiving GC only develop adverse events. Previous randomised controlled trials (RCTs) have applied different primary endpoints, limiting the comparison of treatment effects in meta-analyses and creating an undesired heterogeneity of outcomes. The harmonisation of response assessment is therefore an important unmet need in GCA research. In this viewpoint article, we discuss the challenges and opportunities with the development of new, internationally accepted response criteria. A change of disease activity is a fundamental component of response; however, it is debatable whether the ability to taper GC and/or the maintenance of a disease state for a specific time period, as applied in recent RCTs, should be part of response assessment. The role of imaging and novel laboratory biomarkers as possible objective markers of disease activity needs further investigation but might be a possibility when drugs directly or indirectly influence the levels of traditional acute-phase reactants such as erythrocyte sedimentation rate and C reactive protein. Futures response criteria might be constructed as a multidomain set, but the questions about which domains will be included and what their relative weights will be still need to be answered.

Giant cell arteritis (GCA) is the most common primary vasculitis in older adults. While glucocorticoids (GCs) are still the gold standard for treatment of people with GCA, there have been long-standing efforts to develop GC-sparing strategies, given that up to 85% of patients with GC monotherapy develop adverse events.[1] Tocilizumab (TCZ) is the first agent approved for the treatment of GCA. The phase III registration trial has demonstrated that TCZ, in combination with a 26-week tapering protocol of GC, is superior to placebo plus GC in achieving sustained remission at 52 weeks.[2] This trial was notable not only because of the difference between the intervention and control groups, but also for the primary endpoint being based on sustained remission, which was defined as the achievement of remission from week 12 to week 52 and the adherence to the prespecified GC-tapering protocol. In the absence of internationally agreed response criteria for GCA, the primary outcome of this study has been subsequently used in other phase III studies, including those on upadacitinib (NCT03725202) and (with slight modification) on secukinumab (NCT04930094).

HOW HAS TREATMENT RESPONSE BEEN CAPTURED IN PREVIOUS GCA TRIALS?

It is the scope of response criteria to serve as a primary endpoint in clinical trials as it is the case for the American College of Rheumatology (ACR) response criteria for rheumatoid arthritis (RA) or the Assessment in Ankylosing Spondylitis (ASAS) response criteria for axial spondyloarthritis (axSpA).[3–5] In randomised controlled trials (RCTs) of GCA, different primary endpoints have been applied, limiting the comparison of treatment effects in meta-analyses and creating an undesired heterogeneity of outcome assessments. Besides, it remains debatable which of the definitions have face and content validity to reflect a 'true response' in GCA RCTs.[2 6–15] Harmonisation of response assessment, as it has been done for RA, axSpA and psoriatic arthritis, is an important unmet need in GCA research.

As detailed in figure 1, previous RCTs defined the primary endpoint based on the occurrence and/or number of relapses,[10] the time to first relapse,[6 8 16] the maintenance of remission following GC tapering[2 7 9 11–14] and/or the cumulative GC dose.[10 15] The investigators recognised that almost all people with GCA rapidly improve on initiation of GC therapy, but the recurrence of symptoms and inflammation are common once GCs are tapered.[17] Relapses in GCA are mostly acute and are associated with the risk of ischaemic events necessitating immediate increase of the GC dose (ie, rescue therapy).[18] In RCTs, capturing disease activity at a single, predefined time point (eg, at the end of trial) may be misleading because patients may have flared and reachieved remission after GC dose escalation. A primary endpoint for a GCA trial might therefore account for multiple evaluations throughout the trial or evaluate the duration of relapse-free remission at a specific time point; alternatively, response would focus on the assessment of disease activity, and the evaluations at several time points throughout the trial could be specified separately by the study protocol.

SHOULD GC THERAPY BE A COMPONENT OF THE RESPONSE CRITERIA IN GCA?

It is still crucial to determine whether the ability to taper GC (and over what time period) should be part of response criteria. Rapid reduction of GC increases the likelihood of detecting a significant difference between the intervention and the control groups. While current recommendations of the European Alliance of Associations for Rheumatology (EULAR) target a GC dose of 5 mg prednisone equivalent per day after 1 year,[19] most RCTs applied a scheme leading to the discontinuation

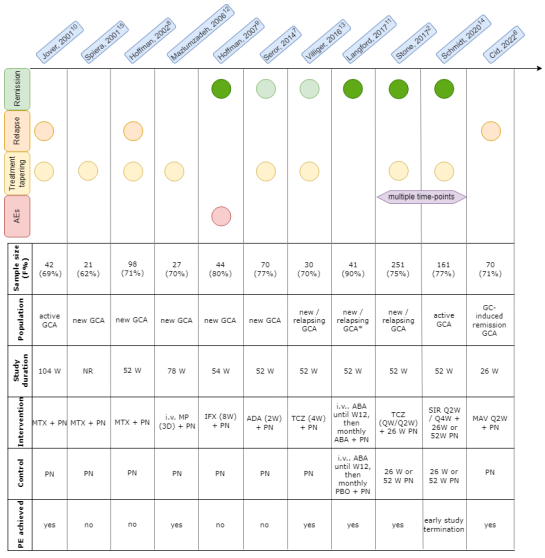

Figure 1 Historical development of primary endpoints of RCTs in GCA. Individual RCTs are depicted with circles pointing to the different components used to define the primary outcomes. Dark green circles indicate a remission definition based on the absence of a relapse/flare, whereas light green circles reflect a specific definition of remission. *With active disease in the previous 2 months. ABA, abatacept; ADA; adalimumab; AE, adverse event; GC, glucocorticoid; GCA, giant cell arteritis; IFX; infliximab; MAV, mavrilimumab; MP, methylprednisolone; MTX, methotrexate; NR, not reported; PBO, placebo; PE, primary endpoint; PN, oral prednisone; Q2W, once every 2 weeks; QW, once a week; RCT, randomised controlled trial; SIR, sirukumab; TCZ, tocilizumab; W, week.

of GCs after 6 months.[2 6 8–11 13–15] A potential downside of not including a GC-tapering schedule in the response criteria is that differing regimens between trials could limit the comparability of their results. However, one might argue that response criteria should reflect change of disease activity independent of GC such that specific GC-tapering parameters should not necessarily be a component of the response criteria. Future studies might even be conducted without GC (given the promising results in other types of vasculitis[20]), and the inclusion of GC in a response definition limits the ability to use the criteria in such trials.

IS THERE ANY ROLE FOR PARTIAL IMPROVEMENT IN THE DEFINITION OF RESPONSE IN GCA RCTS?

Remission is an important primary endpoint in trials, mostly defined as the absence of signs and symptoms of GCA in combination with a normalisation of erythrocyte sedimentation rate (ESR, cut-off of normal in RCTs ranging from 20 mm/hour to 40 mm/hour) and/or C reactive protein (CRP, 1.0–1.5 mg/dL).[16] In the 2018 update of the EULAR recommendations for the management of large vessel vasculitis (LVV), a definition of remission was proposed as the 'absence of all clinical signs and symptoms attributable to active LVV, normalisation of ESR and CRP and no evidence of progressive vessel damage (narrowing or dilation)'.[19] Data from observational studies and real-world practice, however, indicate that partial response can also be a relevant endpoint in GCA.[16] Patients often have partial improvement after having tapered GCs but are not in remission. These patients may report unspecific symptoms such as occasional headache, myalgia and/or low-grade fever, have increased inflammatory markers or imaging signs of arterial inflammation and/or have not been able to taper GCs due to these features.[17] The relevance of partial improvement in the setting of an RCT and the value of this endpoint to patients and physicians still have to be clarified.[21]

SHOULD IMAGING BE PART OF RESPONSE CRITERIA IN GCA?

Imaging techniques to examine inflammatory changes of the vessel wall, particularly ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and ultrasound, have been investigated as possible objective markers of disease activity in GCA.[16] Both methodologies may correlate with clinical activity, and a reduction of PET and ultrasound scores has been observed in patients with clinical improvement.[22–25] While these methodologies may provide additional information on the control of vascular inflammation in drug trials, their value as part of response criteria still remains inconclusive. The main limitation of these imaging techniques is the unclear significance of abnormal findings in patients who are felt to be in remission based on clinical and laboratory parameters. It is still a matter of debate whether patients in remission with positive imaging by PET have worse clinical outcomes than patients with negative imaging results.[24–27]

It is almost impossible to compare imaging findings with histology, particularly with large arteries, and therefore it can only be speculated whether positive imaging results reflect ongoing vascular inflammation, remodelling, healing or another process. While a recent study examining the association of PET and angiographic progression found that arteriographic change was frequently preceded by the presence of FDG-PET activity, the majority of arterial territories where FDG-PET activity was present did not go on to develop vascular changes.[28] These results, however, still need to be confirmed by additional studies.

Magnetic resonance angiography (MRA) and CT angiography (CTA) have played an important role in assessing the large vessel lumen for the presence of stenoses or aneurysms.[29] Some clinical trials have used the development of new lesions in new vascular territories seen by MRA or CTA to be indicative of active disease.[11] However, the certainty of this remains difficult to confirm, given that such changes could also reflect vessel injury with subsequent damage. Similarly, worsening/progression of existing stenoses or aneurysms could also reflect damage rather than disease activity. Distinguishing active disease from permanent damage that is unresponsive to therapy represents one of the most significant challenges in LVV. This uncertainty impacts consideration for how to view the development of new or worsening luminal changes in response criteria for GCA. Moreover, large vessel stenosis or dilatation occurs in a proportion of patients only, and its progression is gradual, which would imply that a high number of patients would be needed if this would be used as a trial endpoint.[30]

WHAT IS THE WAY FORWARD IN THE DEVELOPMENT OF RESPONSE CRITERIA IN GCA?

An international task force endorsed by the EULAR and the ACR is currently working on the development of response criteria for GCA. Apart from the identification of the individual descriptors or elements of the new criteria, several fundamental questions need to be answered: first, should response criteria include a time and treatment component or do these have to be specified separately in the trial design? Second, what is the relationship between response, partial improvement and remission? Lastly, the role of acute-phase reactants needs to be re-evaluated. While in earlier trials, ESR and/or CRP have been an integral part of the primary outcome, TCZ and other novel drugs have a direct

influence on these parameters. In a substudy of the TCZ RCT, it was observed that almost all relapses (92%) in the TCZ groups occurred with a normal CRP, while in patients receiving prednisone plus placebo, only 34% of relapses were associated with a normal CRP.[31] Even though the influence might be minor for drugs not targeting the interleukin (IL)-6 pathway directly, pharmaceutical companies and regulatory agencies might be concerned that investigators become unblinded once they learn the results of acute-phase reactants, which are required to assess the response. In addition, the direct inhibition of ESR/CRP might bias the result in favour of the efficacy of the drug under investigation, which is also problematic.[32] Alternative laboratory parameters which are independent of the IL-6 pathway, such as serum calprotectin or osteopontin, are still a matter of research; also, imaging as a possible alternative indicator of disease activity requires further validation and standardisation.[33 34] Notwithstanding, there is a general wish to include objective measures in the assessment of response to complement symptoms reported by the patient. The assessment of response must also be feasible in clinical practice with an acceptable consumption of resources; otherwise, the conduct of clinical trials will be restricted to a few highly equipped centres which will limit the effective recruitment of patients.

In a recent task force meeting of international GCA experts, a clear structure of the future response criteria did not yet emerge, but discussions included several points elaborated in this viewpoint article. The idea of a multioutcome domain response criteria seems to be the most attractive,[35] but the questions are still which domains would be included (eg, clinical, laboratory, morphological and/or functional imaging, GC treatment or other) and what their weights will be. Subsequent steps of the EULAR–ACR GCA response criteria project will help to answer these questions as well as to identify the individual descriptors, their definitions and weights to outline the future GCA response criteria.

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