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TREAT-TO-TARGET STRATEGIES IN GIANT CELL ARTERITIS AND POLYMYALGIA RHEUMATICA: A SYSTEMATIC LITERATURE REVIEW INFORMING AN INTERNATIONAL TASKFORCE

Keywords: Remission, Vasculitis, Treat to target

E. Hysa¹, M. Bond², L. Ehlers³, D. Camellino⁴, L. Falzon⁵, C. Dejaco^{2,6}, F. Buttgerit³, D. Aletaha⁷, A. Kerschbaumer⁷. ¹San Martino Polylinic, University of Genoa, Italy, Laboratory of Experimental Rheumatology and Academic Division of Clinical Rheumatology - Department of Internal Medicine, Genoa, Italy; ²Hospital of Bruneck (ASAA-SABES), Department of Rheumatology, Bruneck, Italy; ³Charité - Universitätsmedizin Berlin, Corporate Member of Freie, Universität Berlin and Humboldt-Universität zu Berlin, Department of Rheumatology and Clinical Immunology, Berlin, Germany; ⁴Local Health Trust 3, Division of Rheumatology, Genoa, Italy; ⁵University of Sheffield, University of Sheffield, South Yorkshire, United Kingdom; ⁶Medical University Graz, Department of Rheumatology, Graz, Austria; ⁷Medical University of Vienna, Division of Rheumatology, Department of Medicine III, Vienna, Austria

Background: Polymyalgia rheumatica (PMR) and Giant cell arteritis (GCA) are chronic inflammatory diseases. Despite the progress made in the management of these conditions, new unmet needs have emerged particularly in terms of prevention of disease- and treatment-related complications. A treat-to-target (T2T) strategy, which has been well established in other rheumatic diseases, has not yet been developed for PMR and GCA.

Objectives: To retrieve current evidence on T2T strategies in PMR and GCA to inform an international task force (TF) developing T2T recommendations.

Methods: A systematic literature review (SLR) was conducted. Medline, EMBASE, Cochrane Library and clinicaltrials.gov (from inception until May 2022), as well as EULAR/ACR abstract databases were searched (2019-2021). Randomized controlled trials (RCTs) and non-randomized interventional studies published in English and answering at least one of the eleven PICO questions on treatment targets and outcomes, were identified (Table 1). The study selection process, data extraction, data synthesis and risk of bias assessment were conducted independently by two investigators.

Results: Of 7809 screened abstracts, 397 were selected for detailed assessment and 76 papers were finally included (31 RCTs, 8 subgroup/exploratory analyses of RCTs and 37 non-randomized interventional studies). No study comparing a T2T strategy against standard of care was identified. In PMR RCTs, treatment-related outcomes were most commonly used (90.9% of RCTs), specifically in terms of the glucocorticoids (GC) cumulative dose and GC tapering, followed by clinical, laboratory and safety targets (63.3% each). Conversely, the most frequently reported outcomes in RCTs in GCA were prevention of relapses (72.2%), remission, treatment, and safety (66.7 % each). Remission and relapses were variably defined in PMR and GCA RCTs but, in most cases, they comprised a combination of clinical and laboratory parameters (Figure 1). The following predictors of poor treatment response were identified: for GCA, data from RCTs yielded female sex, initial prednisone dose <30mg/day, bad baseline patient-reported outcomes, increased inflammatory markers after the achievement of clinical remission and absence of PMR symptoms at baseline as risk factors for treatment failure and an increased relapse rate. In PMR, no high-quality data predicting clinical outcomes were identified. Finally, in RCTs comparing the outcomes of GCA patients with new onset versus established disease, no differences were found, given that treatment was equal in both groups.

Conclusion: This SLR informed an international TF developing T2T recommendations in PMR and GCA. It provides up-to-date evidence while simultaneously highlighting the gaps in current knowledge about T2T strategies in these diseases.

Table 1. Clinical key questions

1. What are the treatment targets and outcomes in GCA/PMR, and how can they be measured (imaging, lab parameters, clinical, PRO)?
2. Is coming-off GC a treatment target in GCA/PMR, and how quickly should it be achieved?
3. What should be the frequency of monitoring disease state/ adapting therapy? How fast and to what extent should disease activity change before requiring treatment modification?
4. How do comorbidities influence T2T outcomes in GCA/PMR?
5. What are comorbidities related to uncontrolled disease activity?
6. Do targets need to be adapted based on the presence of comorbidities?
7. Is residual disease activity acceptable, and to what extent?
8. How can reaching disease targets, reducing/ preventing treatment side effects, and long-term consequences of disease be balanced in GCA/PMR? What is more important: control of disease activity or prevention of treatment related adverse effects?
9. Can treatment success be predicted?
10. What are the predictors of successful treatment reduction (e.g., duration on target)?
11. Do treatment targets differ over time (early vs. established disease)?

Components used to define remission and relapse in PMR RCTs. Legend: Green circle: Remission and/or relapse used as outcomes but not defined in the study methods. Green circle (with specific components) defined in the study methods. Red circle: relapse (or specific components) defined in the study methods. White circle: component not part of the definition of remission/relapse. Black circle: remission/relapse not used as an outcome. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; Hb, hemoglobin; SAS, morning stiffness; VAS, visual analogue scale. * signs and components of active polymyalgia rheumatica. 1, remission defined by PMR-AS (PMR Activity Score) <10, s.u. and/or.

Components used to define remission and relapse in GCA RCTs. Legend: Green circle: Remission and/or relapse used as outcomes but not defined in the study methods. Green circle (with specific components) defined in the study methods. Red circle: relapse (or specific components) defined in the study methods. White circle: component not part of the definition of remission/relapse. Black circle: remission/relapse not used as an outcome. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound. * Relapse was defined as the return of signs and symptoms and/or as increase of inflammatory markers in GCA patients not receiving GC therapy for at least 1 month. Recurrence was defined as the reappearance of GCA signs and symptoms and/or increase of inflammatory markers in GCA patients not receiving GC therapy for at least 1 month.

Figure 1. Components used to define remission and relapse in PMR and GCA RCTs

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