IgG4-related diseases: state of the art on clinical practice guidelines

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ABSTRACT

Immunoglobulin G4-related diseases (IgG4-RD) are a group of chronic relapsing–remitting inflammatory conditions, characterised by tissue infiltration with lymphocytes and IgG4-secreting plasma cells, fibrosis and a usually favourable response to steroids. In this narrative review, we summarise the results of a systematic literature research, which was performed as part of the European Reference Network ReCONNET, aimed at evaluating existing clinical practice guidelines (CPGs) and recommendations in IgG4-RD. From 167 publications initially obtained from a systematic literature search, only one was identified as a systematic multispecialist, evidence-based, consensus guidance statement on diagnosis and treatment of IgG4-RD, which may be recommended for use as CPG in IgG4-RD.

With the recognition of a limited evidence based in this increasingly recognised disease, the group discussion has identified the following unmet needs: lack of shared classification criteria, absence of formal guidelines on diagnosis, no evidence-based therapeutic recommendations and lack of activity and damage indices. Areas of unmet needs include the difficulties in diagnosis, management and monitoring and the scarcity of expert centres.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is an increasingly recognised immune-mediated chronic relapsing–remitting inflammatory condition, characterised by tissue infiltration with lymphocytes and IgG4-secreting plasma cells, fibrosis and a usually favourable response to steroids. The commonly shared features include tumour-like swelling of involved organs, which in the majority of patients is indolent, particularly in early stages of disease. Pain is usually a consequence of the obstruction or compression due to the presence of mass lesions and their complications. Multiorgan involvement may either be present at the same time (synchronously) or different sites can be affected at various time periods (metachronously). Major presentations of IgG4-RD include type 1 autoimmune pancreatitis, salivary gland disease, orbital disease and retroperitoneal fibrosis. Irrespective of which organ or tissue is involved, the hallmarks of IgG4-RD are lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells, storiform fibrosis and obliterator phlebitis. The clinical suspicion may arise from elevated plasma IgG4 levels, but the definitive diagnosis is based on histology and other cell-based diagnostics as serum concentration may be within the normal range. To prevent fibrosis progression and organ destruction, a treatment of induction and maintenance of remission is necessary. The recommended first-line agents are glucocorticoids. However,
relapses are frequent during tapering, so glucocorticoid-sparing immunosuppressive agents are usually considered, although adequate controlled studies on their efficacy are lacking. Finally, surgery or radiotherapy may be necessary in case of serious organ damage.

In this narrative review, we summarise the results of a systematic literature research, which was performed as part of the ERN ReCONNET project, dedicated to evaluation of currently available clinical practice guidelines (CPGs) or recommendations. Subsequently, clinicians’ and patients’ unmet needs of IgG4RD were discussed.

**METHODS**

**ReCONNET network**

ERN ReCONNET (Rare CONnective tissue and musculoskeletal diseases NETwork) is a European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases funded by the European Union’s Health Program to promote better and safer healthcare, define proper organisational assessment and identify standard and cost-effective pathways for the management of rare and complex connective tissue diseases. The Network includes rheumatologists, internists and immunologists from 26 selected centres in eight different countries across Europe (http://reconnet.ern-net.eu). One of the first network targets was to evaluate currently available CPGs or recommendations in a systematic literature search to identify potential unmet needs in the most relevant rare autoimmune diseases.

**Systematic literature search**

We carried out a systematic search in PubMed and EMBASE based on controlled terms (MeSH and Emtree) and keywords of the disease and publication type (CPGs). We reviewed all published articles in order to identify existing CPGs on diagnosis, monitoring and treatment, according to the Institute of Medicine 2011 definition (CPGs are statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options).

The disease coordinators (DCs) of the ERN ReCONNET for IgG4-RD had assigned the work on CPGs to the healthcare providers (HCPs) involved. Moreover, in order to implement the list of guidelines provided by PubMed and EMBASE search, the group performed also a hand search. A first screening among papers included in the final list (systematic search+hand search) based on title and abstract selected evidence-based medicine guidelines. A general assessment of the CPGs had been performed following the AGREE II tool checklist not for formal appraisal but only to inform discussion. A discussion group composed of DCs (LI and TA) and disease representative (DR) was set for the evaluation of the existing CPGs and to identify the unmet needs.

More precisely, the following search strategy was used to identify publications from the databases:

**Medline (PubMed)**


**EMBASE**

(‘immunoglobulin g4 related disease’/exp OR ‘igg4 related disease’ OR ‘immunoglobulin g4 related disease’) AND (‘practice guideline’/exp OR ‘practice guideline’ OR ‘practice guidelines’/exp OR ‘practice guidelines’ OR ‘clinical practice guideline’/exp OR ‘clinical practice guideline’ OR ‘clinical practice guidelines’/exp OR ‘clinical practice guidelines’ OR ‘clinical practice guidelines as topic’/exp OR ‘clinical practice guidelines as topic’ OR ‘guideline’/exp OR ‘guideline’ OR ‘guidelines’/exp OR ‘guidelines’ OR ‘guidelines as topic’/exp OR ‘guidelines as topic’ OR ‘consensus development’/exp OR ‘consensus development’ OR ‘consensus development conference’/exp OR ‘consensus development conference’ OR ‘consensus development conference’ OR ‘consensus development conference’ OR ‘consensus development conferences as topic’/exp OR ‘consensus development conferences as topic’ OR ‘consensus’/exp OR ‘consensus’ OR ‘recommendation’ OR ‘recommendations’) AND [embase]/lim NOT [medline]/lim.

**STATE OF THE ART ON CPGS**

**Identification of existing CPGs**

The systematic literature search initially identified a total of 165 citations by the ERN ReCONNET central team (figure 1). After performing title and abstract evaluation by disease representatives, eight papers were selected for further review. After full-text review by the disease coordinators, four CPGs were finally selected for further evaluation using full-text assessment,1–4 which were subsequently endorsed by the disease representatives.

**CPG characteristics**

The general characteristics of the four CPGs are summarised in table 1. Of the four preselected publications, only one was identified as a systematic multispecialist, evidence-based, consensus guidance statement on diagnosis and treatment of IgG4-RD, which may be recommended for use as CPG.1 This publication was an International Consensus Guidance Statement on the management and treatment of IgG4-RD, resulting from an expert panel...
of 42 IgG4-RD experts from eight medical specialties (18 gastroenterologists, 13 rheumatologists and 11 other specialists and subspecialists). Although these guidelines are relevant for clinical practice, the evidence level reported in the paper varies between IIb and IV, given the lack of solid and endorsed classification criteria and randomised controlled trials (RCTs) in this field. As a result, there was broad consensus that

► The most accurate assessment of IgG4-RD is based on a full clinical history, physical examination, selected laboratory investigations and appropriate radiology studies.

► Diagnostic confirmation by biopsy is strongly recommended for the exclusion of malignancies and other IgG4-RD mimics.

► All patients with symptomatic, active IgG4-RD and a subset of patients with asymptomatic disease require treatment, some urgently.

► Glucocorticoids are the first-line agent for remission induction unless contraindications are present.

► Some but not all patients require the combination of glucocorticoids and a steroid-sparing immunosuppressive agent from the start of treatment.

► Following a successful course of induction therapy, certain patients benefit from maintenance therapy.

► Re-treatment with glucocorticoids is indicated in patients who relapse off of treatment following successful remission induction. Following relapse, the introduction of a steroid-sparing agent for continuation in the remission maintenance period should be considered.

The remaining three selected GPGs were only reviews or consensus statements on existing data for terminology, pathology and immunopathology of IgG4-RD. They lack accepted methods for systematic review and represent rather expert consensus than real guidelines or recommendation with suboptimal clinical practice use, which may not be recommended as a guideline for use (table 1).

**Table 1** Summary of the evaluation of existing guidelines

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khosroshahi et al, 2015</td>
<td>Systematic review, multiple specialists, guidelines for diagnostic and treatment, so far first real guidelines; very helpful for the physician in clinical practice</td>
<td>1</td>
</tr>
<tr>
<td>Deshpande et al, 2013</td>
<td>Review on existing data for terminology, pathology and immunopathology, no real guidelines, no systematic review; recommendations are lacking, so the usefulness of this paper is limited</td>
<td>2</td>
</tr>
<tr>
<td>Deshpande et al, 2012</td>
<td>Consensus statement on pathology, only expert opinion, no clear systematic review; no systematic methods for formulating recommendations key histopathological features and IgG4 assessment are clearly defined</td>
<td>3</td>
</tr>
<tr>
<td>Stone et al, 2012</td>
<td>Review on terminology based on expert opinion. Although experts from different specialties were present, this is rather expert consensus than a clear recommendation; no systematic guidelines are reported and key messages are not easily identifiable</td>
<td>4</td>
</tr>
</tbody>
</table>
organ damage due to fibrosis and also modulation of the
ising new diagnostic modality. However, more evidence
levels by flow cytometry has recently emerged as a prom-
predictive factors. For example, assessment of plasmablast
have been published on possible diagnostic markers and
in this field are scarce. In the last years, several studies
gold standard for diagnosis, but evidence-based criteria
IgG4 concentrations may be helpful, they have certainly
prevalence of IgG4-RD is probably underestimated, espe-
cially in Europe and North America, where the aware-
ness of its existence may be lower than in Asian countries,
where the disease was initially described. Although serum
IgG4 concentrations may be helpful, they have certainly
lost importance in the diagnosis. Histology is still the
gold standard for diagnosis, but evidence-based criteria
in this field are scarce. In the last years, several studies
have been published on possible diagnostic markers and
predictive factors. For example, assessment of plasmablast
levels by flow cytometry has recently emerged as a prom-
isising new diagnostic modality.
Indications for disease activity and damage are lacking
Similar to other inflammatory rheumatic diseases,
IgG4-RD presents with relapsing–remitting courses that
may eventually result in tissue damage. Therefore, standard-
dised indices for disease activity and damage need to be
developed and validated. In addition, the place and rele-
vance of imaging techniques (eg, ultrasound, CT, MRI
and PET scans) in diagnosis and follow-up of the disease
should be evaluated.
Therapy is not evidence based
Although IgG4-RD frequently represents an indolent condition, treatment is usually required to reduce chronic inflammation and to prevent progressive tissue fibrosis. Furthermore, untreated IgG4-RD with elevated inflammatory markers may lead to secondary AA amyloi-
dosis. Therefore, symptoms and risk of irreversible organ damage due to fibrosis and also modulation of the
underlying chronic inflammatory condition should be
taken into account for treatment decisions. Single-centre
observations suggest favourable responses to glucocorti-
coids, which are regarded as first-line therapy, but relapses are frequently observed during steroid tapering.
Disease-modifying drugs (DMARDs) have proven efficacy
in some cases, but large RCTs investigating the outcome
of various DMARDs are lacking. A recent nationwide
retrospective study showed that rituximab is effective for
both induction therapy and relapse treatment in IgG4-
RD. Hence, RCTs are urgently required in the field, but
difficult to conduct given the rarity and heterogeneity of
the disease. Alternatively, evidence from non-randomised
or uncontrolled studies may also be used for further
developments. In addition, validated tools for treatment
response are lacking and no treat-to-target criteria are
available. Recently, an IgG4-RD responder index has
been developed and an international validation study is
ongoing. To date, this index is the only available instru-
ment to assess IgG4-RD and its use needs to be encour-
aged in clinical practice.
Patient unmet needs
IgG4-RD represents a relatively new disease entity and
awareness of the disease among healthcare providers is
still inadequate and limited to few disease experts. Subse-
sequently, the lag time from symptom onset to diagnosis is
still unacceptably high and may be associated with accrual
of irreversible organ damage before specific treatments
are provided.
Each patient is different in relation to their symptoms
as well as the approach of their care. Most care is also
not evidence based, which may be an additional burden
for the patient as some healthcare systems only support
evidence-based care. Therefore, patients with IgG4-RD
require special attention, especially with respect to inter-
disciplinary dialogue with treating physicians, individual
support from patient representatives as well as guidance
to address the psychosocial impact of the disease.
Centres of expertise for IgG4-RD are currently limited
and not easy to identify by patients. In addition, the
patient support system is still insufficient, as there are
almost no disease-specific patient organisations estab-
lished at the moment on national and international level.
In conclusion, much effort is needed at multiple levels
to meet the specific demands of patients suffering from
IgG4-RD in providing optimised patient care, which may
hopefully be accomplished in the framework of the ERN
ReCONNET.
CONCLUSIONS
IgG4-RD is a relatively new defined clinical entity. There-
fore, formal disease classification and guidelines for
diagnosis and treatment are still widely lacking. Given
the rarity and heterogeneity of this disease, RCT may
only be accomplished in international multicentre trials
with support of pharmaceutical companies. The current

UNMET NEEDS
Clinicians’ unmet needs
The following unmet needs have been identified and
discussed by the DCs and DRs:
Lack of shared classification criteria
There is no international consensus on classification
criteria for IgG4-RD. Therefore, development of valid-
dated classification criteria should be the first step to
guide clinicians in stratifying patients and to provide the
basis for further collaborative and comparative research
studies in the field. In this sense, the European League
Against Rheumatism (EULAR) and American College of
Rheumatology (ACR) are currently jointly supporting a
Task Force for the development of classification criteria
for IgG4-RD that will hopefully be available in the near
future.
No formal guidelines for diagnosis available
Diagnosis of IgG4-RD is challenging, given the hetero-
gegeneity of clinical symptoms and laboratory results. The
prevalence of IgG4-RD is probably underestimated, espe-
cially in Europe and North America, where the aware-
ness of its existence may be lower than in Asian countries,
where the disease was initially described. Although serum
IgG4 concentrations may be helpful, they have certainly
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in this field are scarce. In the last years, several studies
have been published on possible diagnostic markers and
predictive factors. For example, assessment of plasmablast
levels by flow cytometry has recently emerged as a prom-
isising new diagnostic modality. However, more evidence
in this field is necessary to provide the basis for standard-
ised algorithms in the diagnostic process. Further studies
are required that need to be performed in an interna-
tional collaborative setting, including all involved disease
specialists, that is, rheumatology, gastroenterology,
vascular medicine, surgery, radiology, pathology and clin-
ic immunology.
Indices for disease activity and damage are lacking
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dised indices for disease activity and damage need to be
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Although IgG4-RD frequently represents an indolent condition, treatment is usually required to reduce chronic inflammation and to prevent progressive tissue fibrosis. Furthermore, untreated IgG4-RD with elevated inflammatory markers may lead to secondary AA amyloi-
dosis. Therefore, symptoms and risk of irreversible organ damage due to fibrosis and also modulation of the
development of disease classification criteria by the EULAR and ACR task force will be the first step to harmonise terminology and to provide the basis for further collaborative studies on diagnostic recommendations and treatment guidelines, which need to be endorsed by scientific international societies (ie, EULAR, ACR). In the absence of RCTs, the implementation of non-randomised pilot studies will help to increase the level of evidence of therapeutic guidelines.

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