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Guidelines for biomarkers in autoimmune rheumatic diseases - evidence based analysis

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ABSTRACT

Autoimmune rheumatic diseases are characterised by an abnormal immune system response, complement activation, cytokines dysregulation and inflammation. In last years, despite many progresses in managing these patients, it has been shown that clinical remission is reached in less than 50% of patients and a personalised and tailored therapeutic approach is still lacking resulting in a significant gap between guidelines and real-world

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practice. In this context, the need for biomarkers facilitating early diagnosis and profiling those individuals at the highest risk for a poor outcome has become of crucial interest. A biomarker generally refers to a measured characteristic which may be used as an indicator of some biological state or condition. Three different types of medical biomarkers has been suggested: i. mechanistic markers; ii. clinical disease markers; iii. therapeutic markers. A combination of biomarkers from these different groups could be used for an ideal more accurate diagnosis and treatment. However, although a growing body of evidence is focused on improving biomarkers, a significant amount of this information is not integrated on standard clinical care.

The overarching aim of this work was to clarify the meaning of specific biomarkers during autoimmune diseases; their possible role in confirming diagnosis, predicting outcome and suggesting specific treatments.

1. Introduction

Autoimmune rheumatic diseases are characterised by an abnormal immune system response, complement activation, cytokines dysregulation and inflammation [1]. These heterogeneous disorders may affect various organs, and although their clinical presentations may be different, these diseases share significant genetic risk factors and common regulatory mechanisms [2]. Environmental and female-associated factors also play pathogenic roles in development of autoimmune diseases [1,2]. In last years, despite many progresses in managing these patients, it has been shown that clinical remission is reached in less than 50% of patients and a personalised and tailored therapeutic approach is still lacking resulting in a significant gap between guidelines and real-world practice [3,4]. In this context, the need for biomarkers facilitating early diagnosis and profiling those individuals at the highest risk for a poor outcome has become of crucial interest [5,6]. A biomarker generally refers to a measured characteristic which may be used as an indicator of some biological state or condition [7]. Three different types of medical biomarkers have been suggested: i. mechanistic markers; ii. clinical disease markers; iii. therapeutic markers [8]. In the first group, subcellular changes may lead to alterations in proteins detectable as biomarkers and reflecting the ongoing cellular process and manipulated signalling pathways [9]. In the second group, the disease development is associated with the changes in proteins that are detected by proteomics, defining the clinical disease markers, which indicate state of progression, severity and location of the disease [10]. In the third group, the treatment of a disease may point out therapeutic biomarkers, associated with a specific changing pattern after the drug administration [11]. Taking together these observations, a combination of biomarkers from these different groups could be used for an ideal more accurate diagnosis and treatment. However, although a growing body of evidence is focused on improving biomarkers [7–11], a significant amount of this information is not integrated on standard clinical care. (See Table 1.)

The overarching aim of this work was to clarify the meaning of specific biomarkers during autoimmune diseases; their possible role in confirming diagnosis, predicting outcome and suggesting specific treatments.

Table 1
The Table summarizes the elaborated statements from systematic literature review and activities of working groups.

Statements	LoE
RA Working Group	
In a population-based setting, higher level of anti-cyclic citrullinated peptide (anti-CCP), defined as ≥3-fold the ULN, might be more clinically useful for RA diagnosis.	2b
RF positivity together with very high levels of aCCP might be useful to discriminate RA patients from other rheumatic diseases.	3
High levels of anti-CCP and/or RF seem to correlate with higher disease activity and worse radiographic progression over time. High titre aCCP and RF are correlated with better response to rituximab, while only very high aCCP titers seem to be associated with better response to abatacept.	2b
Anti-CarP antibodies may serve as predictors of more severe radiographic progression in RA and potentially associated with more severe disease course	2b
In RA, the possible role of MBDA in predicting disease course and response to treatments is still controversial.	5
SpA Working Group	
Although enthesitis may be considered a clinical marker of PsA, there is no evidence showing that its presence at baseline predicts the response to different bDMARDs (TNFis, IL17is, IL12/IL23is).	5
Although data available on biomarkers for predicting therapeutic response in SpA are scarce, CRP in clinical practice may be useful in predicting TNFis response.	2b
SSc working group	
Anti-topoisomerase 1 antibody is a biomarker for faster progression of SSc-ILD	2b
KL-6, SP-D, CCL18 may be considered as biomarkers for short-term progression of SSc-ILD.	3b
The DETECT algorithm is useful to identify SSc patients at higher risk for PAH who should undergo RHC.	2a
High levels of plasma CXCL4 may predict development of PAH in SSc patients.	2b
High levels of serum Anti-AT1R and Anti-ETAR antibodies may predict development of PAH in SSc.	2b
SLE working group	
There is no evidence that a negative serology predicts a successful withdrawal of therapy in SLE patients (with or without nephritis) in clinical remission.	5
In lupus nephritis, negative serology does not predict a successful withdrawal of therapy.	3b
APS working group	
The addition of anti-domain I to laboratory classification criteria seems to increase the risk of thrombosis.	5
There is no evidence that anti-domain I can substitute anti-beta2GPI I.	5
The presence of anti-PS/PT seems to increase the risk of clinical manifestations of APS.	5
The presence of anti-PS/PT seems to identify very few patients with the so called seronegative APS.	5
pSS working group	
The predictive value of CXCL13 in pSS, for both poor prognosis and therapeutic response, remains to be clarified.	2b
The predictive value of baseline BAFF levels for lymphoma development and therapeutic response to RTX should be further assessed.	2b
The clinical utility of the presence of GC-like structures, in MSGs, to predict lymphoma development should be further assessed with standardization of technique and multicentre studies given the relatively low incidence of lymphoma.	3b

2. Methods

2.1. Aims of the project

The overarching aim of this workshop is to clarify the meaning of specific biomarkers during autoimmune diseases; their possible role in confirming diagnosis, predicting outcome and suggesting specific treatments. The general methodology based on a Delphi Technique-based aimed at producing, starting from the results of a systematic review of available literature, a set of statements summarising the consensus among the Experts, as previously reported [12]. This systematic review has been designed to be included in an International project named "*Clinical and biological biomarkers in conventional and/or biological therapies. From pathology to treatment: what evidence in rheumatic and autoimmune diseases? 2th International workshop*" aimed to update some features in management of patients affected by autoimmune disease. As a part of an International project, a Scientific Committee composed by a group of experts and bibliographic fellows identified some relevant clinical questions on biomarkers in autoimmune diseases, needing further and updated clarifications according to available scientific evidence and joined Experts' opinion. These invitations were a consequence of the individuals' contributions to the specific fields included in the topics of the meeting as well as deliberations among members of the steering committee. Six autoimmune diseases were selected and evaluated: rheumatoid arthritis (RA), spondyloarthritides (SpA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), primary Sjogren's syndrome (pSS). These topics were developed and updated throughout an extensive bibliographic review by the Steering Board, after joining common limits and methods of search. For each selected topic, preliminary statements based on available scientific results have been presented in accordance with their level of evidence, discussed, eventually reformulated, and voted through a Delphi-method during a Consensus involving a panel of International Experts. Statements supported by ≥ 66% of votes were accepted as final statements, while the others were rejected outright. This project has been concluded in Italy on October 6-7, 2017.

2.2. Search design

For each of these 6 topics, a systematic literature search was performed in indexed international Journals (Medline via Pubmed, Scopus, Cochrane database). The Scientific Committee decided to analyse the literature from July 1, 2007 – July 1, 2017. The choices of temporal limits, online databases and methodology were originally discussed and shared by participants in order to gain homogeneous results.

2.3. Search strategy

The search strategy combined indexed and free-text terms, interventions and outcomes of interest in Medline via Pubmed, Scopus, Cochrane database, as requested for each single topic. PICO strategy was also joined as shared rephrasing strategy across working groups, along with pre-defined "Population", "Intervention", "Comparison", "Outcomes", as requested by single topic research question. The main search was thus formulated using a string of relevant terms of research. In addition, the main keywords were used in different combinations in order to improve the sensitivity of the search strategy. The bibliography of relevant articles was also hand-searched for identification of other potentially suitable studies.

2.4. Eligibility criteria

Included studies were full-text manuscripts in English language conducted in adult patients with autoimmune diseases. To be included in the final analysis, studies had to meet the following joined inclusion criteria: 1) study design: systematic review and meta-analysis, randomised controlled trial (RCT), quasi-RCT (trials in which allocation to treatment was made by alternation, use of alternate medical records, date of birth or other expected methods), observational cohort studies or case series; 2) data concerning population, intervention, comparison and outcomes were requested for each single selected topic. Narrative reviews, editorials, scientific conference abstracts, case reports and pre-clinical studies have been excluded from the purpose of this work. Papers retrieved by literature search but reporting insufficient data according to selected PICO strategy were excluded from the review. The hierarchy of study types was indicated by levels of evidence suggested by Oxford University (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/).

2.5. Study identification and data extraction

In each group working on a single topic, full-text articles were screened and selected analysing titles and abstracts by bibliographic fellows, then independently verified by corresponding senior reviewers. After the screening phase, the bibliographic fellows also independently evaluated the selected abstracts and the full-text of these studies to determine eligibility according to the eligibility criteria. Any uncertainties and/or disagreements were resolved by discussion until reaching a final consensus. Data extraction was also performed by bibliographic fellows and independently verified by corresponding senior reviewers. After that, the results of the analysis of literature were summarised, presented, and further inputs were obtained from expanded working groups with other authors. Conflicting results were analysed by discussion taking into account quality of assessed studies until reaching an agreement into the single working group. The statements were thus formulated according to results and quality of evaluated works. Further disagreements were resolved by discussion until reaching a final consensus. In the subsequent plenary session, the statements were subjected to be voted as 'yes' (agreement) or 'no' (disagreement) from the entire panel of Experts. Statements supported by ≥ 66% of positive votes were accepted while the others were rejected outright. At this final stage, only suggestions for improvements of clarity of wording or addressing redundancies were considered, while any change to the meaning was not accepted.

3. RA working group

To date, recognition and better definition of disease-specific biomarkers, easily and routinely detectable in patients serum samples, could be relevant for diagnostic and prognostic purposes in the view of a more patients' tailored approach, regardless of the underlying condition. Anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) are well recognized clinically relevant biomarkers in rheumatoid arthritis (RA) patients [13]. Their pathogenic role has been well characterized, being detectable in the serum in pre-clinical phase many years before clinical presentation of the disease. Moreover, both biomarkers have been included in the new 2010 RA classification criteria into a score-based algorithm where both qualitative (negative versus positive) and quantitative (low level versus high level) evaluations have been inserted, with high level (predefined as ≥3 times the ULN for the laboratory test and assay) having greater weight in substantially contributing to RA diagnosis [14]. In the 2016 update of EULAR recommendations for RA management, either presence and levels of RF and/or ACPA have been listed among several other prognostic factors to be considered during therapeutic management, too. Moving from this starting point, it could be clarified whether a better definition of such biomarkers (high versus low serum levels) might help clinicians in term of discriminative ability in diagnostic accuracy (as diagnostic and differential diagnostic tool) and prognostic stratification (disease course, radiographic damage, response to therapy). In other words, throughout an extended systematic review on the topic in line with joined pre-specified limits and settings, the clinical meaning of "level criterion" of

"serology" item has been investigated in light of diagnostic and prognostic purposes (see corresponding PICOs rephrasing in Table 1/in the attached files). Any case, when interpreting lab results of RA serum biomarkers, several concerns might be taken into account justifying contrasting data across studies: lack of harmonization and standardization of RF and ACPA tests (different methods, cut-off levels, reference materials); assessment of different RF isotypes (IgG, IgA, IgM) and ACPA specificities; disease and demographical characteristics of enrolled RA patients (ethnic and genetic background of target populations, disease duration, environmental exposition); lastly, when considering the impact of biomarkers on prognosis, previous and current treatment itself might be a confounding factor, too. Moreover, as a further source of heterogeneity and variability, different definitions of high and low levels of either RF and/or ACPA have been proposed across studies, mostly in accordance to EULAR/ACR 2010 classification criteria (3 times higher the cut off values) [14].

3.1. Diagnostic purposes, the role of anti-CCP

3.1.1. In a population-based setting, higher level of anti-cyclic citrullinated peptide (anti-CCP), defined as ≥3-fold the ULN, might be more clinically useful for RA diagnosis. LoE 2b

Two population-based studies assessed in large unselected cohorts the discriminatory capacity of anti-CCP in diagnosing RA for either prevalent (cross-sectional analysis) and incident (prospective analysis) cases [15,16]. These studies offered the unique advantage of testing such biomarker in numerous healthy (independently of any previous/current sings and/or symptoms of arthritis or any previous lab measurement) rather than selected subjects, like blood donors or high-risk populations (symptom-free first-degree relatives of RA patients, patients with arthralgia, patients suffering from other autoimmune diseases). In both studies, high anti-CCP levels have been defined in accordance to ACR/EULAR 2010 classification criteria. In the study by Hensvold, high versus low anti-CCP2 titres were associated with increased specificity for prevalent RA with only minor decrease in sensitivity (98% and 66% and 99% and 62% with positive anti-CCP2 and high anti-CCP2 cut-off, respectively). In the study by Demourelle et al [15], when prevalent cases were considered (established RA patients), the higher the adopted anti-CCP cut-off levels, the better the specificity (93.1% using standard cut-off level, 97.2% with ≥ 3 X standard cut-off level for anti-CCP3 assay). Despite this, it remains debatable whether a single assay with a common threshold could be considered optimal for all clinical settings.

3.1.2. RF positivity together with very high levels of anti-CCP might be useful to discriminate RA patients from other rheumatic diseases. LoE 3

We identified 6 research articles that compared anti-CCP test in term of discriminative diagnostic performance in patients suffering from RA or other RA-mimicking rheumatic or non-rheumatic diseases [17–22]. All of them have case-control design involving as control population patients with non-RA inflammatory and non-inflammatory rheumatic diseases (osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, spondyloarthritis, systemic sclerosis, crystal-induced arthritis, infectious arthritis, systemic sclerosis, fibromyalgia, and/or other related conditions) [17–22]. The underlying hypothesis is that elevated anti-CCP levels, as more specific RA markers respect to RF, can help in better supporting the differential diagnosis of RA and the above indications. In the largest study by Pietrapertosa, specificity and sensitivity of anti-CCP2 antibodies measured by ELISA were tested in 787 patients with RA, 1024 patients with other autoimmune/inflammatory rheumatic disease and 401 subjects without autoimmune rheumatic diseases (osteoarthritis and fibromyalgia) [22].Using ROC curve analysis, the cut-off value of 2.8 U/mL for anti-CCP2 had the highest diagnostic accuracy for distinguishing between RA patients and both control cohorts, but a value of anti-CCP2 15 U/mL (3 fold the manufacturer cut-off) was associated with a significant increase in the likelihood of RA disease. In addition, in a Chinese population, the combination of high titre anti-CCP antibodies (≥100 RU/ml) with a concomitant positive RF test exhibited the greatest diagnostic specificity, especially in the early stage of the disease, respect to single positive RF and/or anti-CCP or double positive or RF+ and low positive anti-CCP [20]. Contrasting results come from a French and Korean studies, where anti-CCP level (high versus levels) did not offer further information in discriminating RA from other non-RA diseases: anti-CCP positivity resulted significantly more prevalent in RA patients, whereas high titres anti-CCP, when positive, did not substantially differ across rheumatic RA and non-RA conditions [18,21].

3.2. Prognostic purposes, RF and anti-CCP

High levels of anti-CCP and/or RF seem to correlate with higher disease activity and worse radiographic progression over time. High titre anti-CCP and RF are correlated with better response to rituximab, while only very high anti-CCP titres seem to be associated with better response to abatacept. LoE 2b.

3.2.1. Radiographic progression

Globally, high levels of either RF and/or anti-CCP were significantly associated with worst deterioration over time in RA patients [23–31]. In the study by Syversen et al. among 125 established RA patients, anti-CCP considered either as categorical and quantitative parameter was significantly associated with radiographic progression according to the van der Heijde modified Sharp score of the hands at 10-year assessment [23]. Anti-CCP (OR 4.0; 95% CI 1.6 to 10.0) was the strongest independent predictor of radiographic progression, in a level-dependent fashion: respect to anti-CCP-negative patients, low to moderate (25–200 U/ml) and high levels (> 200 U/ml) anti-CCP subjects were more likely to develop radiographic progression over time (corresponding Odds Ratios/OR being 2.6, 95% CI 0.9 to 7.2 and 9.9, 95% CI 2.7 to 36.7, respectively). Higher cut-off RF levels did not change the model, without improving or weakening the prognostic effect of anti-CCP. Conversely, in a cohort of Japanese early RA patients (disease duration < 2 years), median total Sharp score at 2 years did not significantly differ among baseline low-titre (median score [IQR] 23.0 [8.0, 47.3]) versus high-titre (21.5 [7.5, 52.0]) anti-CCP groups; nevertheless both subgroups substantially differed respect to anti-CCP negative patients (2-year median Sharp score [IQR] 6.0 [2.0, 12.0], p = 0.00001 versus low- anti-CCP p = 0.00001 versus high-anti-CCP) [27]. Different target populations (established versus early disease in divergent ethnic background), outcome time-points (10-year versus 2-year), anti-CCP cut-off pre-defined levels, might account partly for divergent results between these 2 studies [30]. A level-dependent effect on structural outcome was confirmed for RF-titres too, in line with Van der Linden et al. study [25]. Regardless of the given definition, high RF levels (defined as > 3 cut-off value, as in the 2010 ACR/EULAR classification criteria or RF > 50 units/ml/RF50, in line with definition given by previous studies) were significantly associated with a higher risk of radiographic progression over 7 years in 686 RA patients; nevertheless the association between high RF level and RA severity was not as strong as that between anti-CCP positivity and RA severity, with significantly greater progression rate for ACPA+ versus both high RF levels definitions. Similarly, pooled data from five clinical trials demonstrated a significant RF level-dependent effect (RF−, RF low+, RF high+) on radiographic damage (proportion of progressors and of rapid progressors) in the study by Aletaha et al. after adjustment for relevant and confounding parameters like disease duration, baseline damage, baseline CRP and baseline ESR [28]. In addition, even in case of DMARDs-induced disease control, high level ACPA (> 48 U/mL, as defined through ROC curve) resulted the strongest independent predictor of clinically relevant radiographic progression in a real-world Japanese prospective study. Possibly, an additive effect between ACPA and RF could be taken into consideration when considering RA structural

damage: only in ACPA positive RA patients, TC-detected erosion burden at hands (number and size of erosions) was cross-sectional associated with RF-levels; thus, RF might act as a structural damage enhancer only in ACPA-positive patients in a dose-dependent manner [26].

3.2.2. Disease activity

Higher anti-CCP and RF concentrations resulted associated with greater disease activity over time along with lower chance to achieve sustained remission in men with established RA mainly under csDMARDs background [32,33]. Similarly, baseline low RF and anti-CCP levels (arbitrarily chosen by the authors) were independently predictive of clinical remission and low disease activity achievement at 12 months in 90 Romanian RA patients starting their first TNFi. High anti-CCP titres significantly correlated with higher RF levels, DAS28 score and more severe morning stiffness duration in a Chinese population by Li et al [20].

3.2.3. Response to therapy

The systematic review by Salgado included two studies considering the impact of RF levels (high versus low) on TNFi response: only the one by Klaasen er al enter our review due to publication date [34,35]. Among 101 RA patients eligible to infliximab, presence and high (> 100 UI/mL) levels of RF-IgM significantly and positively correlate with primary response to therapy at 16 weeks, while high RF-IgG and RF-IgA did not. On the contrary, in the study by Salgado no significant differences across 50th, 25th and 75th percentiles of baseline IgM RF titres were observed between responders and non-responders (EULAR response criteria at 24 weeks) in a combined cohort of 3 Spanish centres experience [36]. Such contrasting results for RF levels and TNFi response are in line with previous published reports on the topic [37]. High levels of aCCP (> 400 UI/mL) resulted significantly associated with greater probability of achieving ACR20 response after 16 weeks of adalimumab medication in a cohort of 70 RA patients [38]. Similarly, among 108 RA patients those with baseline anti-CCP titres > 300 UI/mL were more likely (more than 3 times) to gain major EULAR response 6 months after the first rituximab cycle after failure of at least one TNFi in the retrospective analysis by Narvaez et al. [39]. Finally, from the post-hoc analysis of the AMPLE trial as a head-to-head comparison between adalimumab and abatacept on a MTX background in MTX-IR patients, baseline anti-CCP2 positivity was associated with a better clinical response to both ABA and ADA. Nevertheless, only in ABA group, patients with the highest (fourth quartile, corresponding to very high levels, 1060–4894 AU/mL) vs lower CCP2 concentrations (Q1) had better clinical response with ABA; this association was not observed in ADA group. Despite not designed and powered for such comparison, there was no inter-group difference in term of clinical response between the highest quartile group patients belonging to ADA or ABA group [40].

In RA patients, auto-antibodies like RF and ACPA represent the hallmark of the break of immune tolerance, accompanying and justifying both the onset and the burden of the disease itself. Very recently, the “level criterion” of such biomarkers entered into both classification and prognostic stratification criteria. In line with retrieved scientific evidences, joined by an international panel of expert rheumatologists, a better definition of either RF and ACPA in term of high versus low levels might add relevant information for diagnostic and prognostic purposes, thus supporting clinicians for a more specific disease recognition and prognostic stratification. To date, efforts should be pointed out to harmonize and standardize biomarkers detection in order to allow comparison and generalization of results either at a research level, and in the everyday clinical setting.

3.3. Anti-CarP in predicting more severe RA course

3.3.1. Anti-CarP antibodies may serve as predictors of more severe radiographic progression in RA and potentially associated with more severe disease course. LoE 2b

Antibodies against carbamylated proteins (anti-CarP antibodies), recognising proteins post-translationally modified by a process of carbamylation, have been recently detected in rheumatoid arthritis (RA) [41–43]. In this systematic review of literature, we investigated the prognostic role of anti-CarP antibodies in predicting more severe RA course. After screening titles and abstracts, 5 observational studies were retrieved and included in the review [44–48].

Shy et al assessed anti-CarP in sera from 571 RA patients by Leiden EAC cohort and 305 healthy controls [44]. Authors reported 45% of RA patients were positive for IgG anti-CarP antibodies and 43% positive for IgA anti-CarP antibodies. Furthermore, anti-CarP antibodies were associated with a more severe radiographic damage over 7 years, analysing all enrolled patients. Of note, anti-CarP IgG antibodies were associated with a more severe radiological progression also in ACPA-negative RA [44]. These findings have been replicated in subsequent studies, assessing anti-CarP antibodies to be an independent predictor of radiographic progression [45,46]. Ajeganova et al. assessed 576 Swedish and 628 Dutch patients and observed anti-CarP antibodies were associated with more severe radiographic progression over 8 years in all included and ACPA-negative RA patients [45]. Similarly, Brink et al reported a more severe radiographic damage in 42.2% of RA patients positive for such antibodies over 2 years [46]. Anti-CarP antibodies have been also correlated with subclinical atherosclerosis and mortality in RA patients [47,48]. In the study by Spinelli et al, the association between anti-CarP antibodies and measures of endothelial dysfunction, used as markers of subclinical atherosclerosis, was described in 50 RA patients [47]. Finally, in a Spanish cohort of 331 RA patients, Vidal-Bralo et al. reported a correlation between anti-CarP antibodies and mortality in RA over a period of 9 years follow-up [48].

Despite providing a synthesis of available literature, our systematic review is impaired by different limitations, mainly due to lack of standardization of tests analysing anti-CarP antibodies and different RA characteristics across evaluated studies (i.e. different disease durations and applied classification criteria).

3.4. The possible role of MBDA in RA management

3.4.1. In RA, the possible role of MBDA in predicting disease course and response to treatments is still controversial. LoE 5

Multi-biomarker disease activity (MBDA) test has been developed evaluating serum levels of 12 proteins associated with RA disease activity [49,50]. In this systematic review of literature, we investigated the role of MBDA in RA, assessing its predictive role of radiographic progression and response to treatments. After screening titles and abstracts, 6 observational studies were retrieved and included in the review [51–56].

Conflicting results are published assessing the predictive value of MDBA for radiographic progression. In the study by Bakker et al., MBDA was not identified as predictor of radiographic progression over 2 years analysing 120 sera from CAMERA study, despite the association with disease activity [51]. Similarly, analysing sera and outcomes of 171 RA patients enrolled in the DRESS study, MBDA score was not predictive of radiographic progression, neither of successful tapering or subsequent flare, in patients who tapered TNFi [52]. In contrast, Hambardzumyan et al. reported MBDA score was an independent predictor of radiographic progression, analysing 235 RA patients from SWEFOT trial, after 1 year of follow-up [53]. Furthermore, associations between MBDA score and imaging findings of radiographic damage, were investigated in 52 RA patients enrolled in HURRAH trial, by using magnetic resonance imaging (MRI), ultrasonography (US), computed tomography and radiography. Despite the fact that the MBDA score

poorly correlated with MRI/US indexes of inflammation, elevated values were determined in patients characterised by more severe radiographic damage [54].

Analysing MBDA and response to treatment, Hambardzumyan et al. described the MBDA to be predictive for optimal add-on treatment in non-responder RA patients [55]. Authors assessed data from 157 patients enrolled in SWEFOT trial, after 3 months of methotrexate (MTX) therapy. A significant percentage of patients characterised by a low MBDA score experienced a good clinical response to subsequent triple therapy (MTX + sulfasalazine + hydroxychloroquine), whereas in patients displaying a high MBDA score, a significant percentage experienced a good clinical response to subsequent combination therapy with TNFi (MTX + infliximab) [55]. Finally, in the analysis of RETRO study MBDA scores were investigated to be predictive of disease relapse. RETRO was a phase-3, multicentre, randomised, open, prospective, controlled, parallel-group study in patients were allocated to continue conventional and/or biological DMARD regimen at full dose for 12 months, to reduce the dose of all conventional and/or biological DMARDs by 50% or to reduce the dose of all conventional and/or biological DMARDs by 50% for the first 6 months before to entirely stop all DMARDs. The results showed that higher values of MBDA scores in patients experiencing disease relapse after tapering and/or stopping conventional and/or biological DMARDs treatment, allowing a prediction of relapse in more than 80% of the patients [56].

Future specific designed and adequately powered studies with a longer follow up are needed to fully clarify the role of MBDA in management of RA patients, in predicting radiographic progression as well as response to therapeutic strategies.

4. Spondyloarthritides working group

The spondyloarthritis (SpA) complex includes a group of inflammatory rheumatic diseases with peculiar clinical and radiological features including sacroiliitis, enthesitis, and dactylitis [57]. Among SpA, psoriatic arthritis (PsA) is characterized for a broad and heterogeneous spectrum of clinical features and courses [58,59]. In some cases, PsA can occur with peripheral enthesitis, particularly Achilles tendinitis, and/or dactylitis [60,61]. In the last decades, an increasing attention has been paid to the erosive and deforming course of PsA (40%–60% of patients) [62]. The identification of clinical and biological predictors of response to different biological disease-modifying anti-rheumatic drugs (bDMARDs) might help clinicians to make evidence-based decisions that maximise the benefits from treatment by targeting subsets of patients. In addition, this approach could also improve the cost/benefit and benefit/risk ratios in patients selected to start bDMARDs treatment [63].

4.1. Although enthesitis may be considered a clinical marker of PsA, there is no evidence showing that its presence at baseline predicts the response to different bDMARDs (TNFis, IL17is, IL12/IL23is). LoE 5

Enthesitis is the inflammation of the insertion of tendons and ligaments into the bone and represents a hallmark of PsA and SpA [64]. It can be considered among the first signs of PsA, occurring independently of arthritis [60]. The role of enthesitis as a predictor of treatment response in ankylosing spondylitis (AS) has been well defined in 2011 by Vastesaeger et al. [65]. Thereafter, in 2013, in a retrospective study, Spadaro et al. and co-workers showed that in AS patients treated with adalimumab, etanercept or infliximab, the probability of obtaining partial remission was significantly lower when enthesitis was present at baseline [66]. In PsA patients, there are no studies evaluating the role of enthesitis as an independent clinical biomarker predicting the response among different bDMARDs (TNFis, IL17is, IL12/IL23is).

4.2. Although data available on biomarkers for predicting therapeutic response in SpA are scarce, CRP in clinical practice may be useful in predicting TNFis response. LoE 2b

Only few articles addressed the potential role of soluble biomarkers in prediction of treatment response to TNFis in SpA patients. The majority of these studies were characterised by a weak methodology, mainly due to low power or lack of power calculation and an uncontrolled design. Amongst the potential biomarkers, baseline serum levels of matrix metalloproteinase-3 (MMP-3) [67,68], serum type I collagen C-telopeptide (sCTX) [69], complement fraction C3 [70], serum amyloid A (SAA) [71], anti-drug antibodies (ADAbs) [72], and IL-6 [73] have been reported to predict treatment response in individual studies. Moreover, two well-designed sub-studies of RCTs evaluated the predictivity of a large pool of soluble biomarkers in AS and PsA [74,75]. In particular, baseline levels of insulin, apolipoprotein C3, leptin, haptoglobin, IL-6, osteocalcin, procollagen type 1 amino-terminal propeptide (P1NP) and deoxypyridinoline were associated with ASAS20 response at week 14 in AS patients while baseline levels of adiponectin, prostatic acid phosphatase (PAP) and vascular endothelial growth factor (VEGF) predicted at least two out of the three clinical endpoints (ACR20, DAS28, PASI75) after 14 weeks in PsA patients. The results of the systematic review showed that only higher baseline C-reactive protein CRP values were consistently reported to predict response to treatment with TNFis in SpA patients, although this evidence relies mainly on observational studies [71,74,76] and only one RCT [73].

5. SSc working group

SSc has the highest fatality rate among connective tissue diseases and is characterized by cellular and humoral immunological abnormalities, fibroproliferative vasculopathy, and fibrosis of the skin and various internal organs. Pulmonary involvement, including both interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) is currently the primary cause of morbidity and mortality in SSc [77]. The course of ILD is highly variable, and patients may develop severe and rapidly progressive interstitial lung involvement during the early phase of the disease, while others may have a limited and non-progressive course [78–81]. The clinical course of untreated PAH is in most cases rapidly progressive leading to respiratory failure or death within 2–3 years after it becomes clinically detectable [82]. In this context, the identification of biomarkers for assessing certain phenotypes associated with an increased risk of developing severe and rapidly progressive ILD and/or PAH is extremely important [83]. At present, despite intense investigation, only a few biomarkers for SSc have been fully validated and widely accepted. On this background, five statements were formulated and voted.

5.1. Anti-topoisomerase 1 antibody is a biomarker for faster progression of SSc-ILD. LoE 2b

Anti-topoisomerase 1 antibody is directed against DNA topoisomerase I and is strongly associated with the diffuse form of SSc and with the development and/or faster progression of ILD. The Genetics versus Environment in Scleroderma Outcome Study (GENISOS), based on a prospective, observational cohort of 266 patients with early systemic sclerosis, confirmed that the presence of anti-topoisomerase 1 antibody was the only variable associated with differential forced vital capacity (FVC) levels, predicting the rate of decline in FVC within the first 3 years of follow-up [80]. Subsequently, a study cohort consisting of 398 consecutive SSc patients with follow-up for up to 15 years confirmed that anti–topoisomerase 1 antibody remained a significant predictor of the development of clinically significant pulmonary fibrosis together with other variables such as dcSSc, lower FVC, and lower diffusing lung capacity for carbon monoxide (DLCO). In this study, SSc-ILD was

confirmed by high-resolution computed tomography, and clinically significant SSc-ILD was defined as FVC or DLCO ≤55% predicted or a documented decline in FVC or DLCO of ≥15% [84]. However, there is no consensus for the definition of ILD progression.

5.2. KL-6, SP-D, CCL18 may be considered as biomarkers for short-term progression of SSc-ILD. LoE 3b

Krebs von den Lungen-6 (KL-6), surfactant protein-D (SP-D) and CC-chemokine ligand 18 (CCL18) are proteins produced and secreted by alveolar type II epithelial cells and alveolar macrophages, and were found to be increased in the serum of SSc patients compared to healthy subjects, and were further increased in SSc-ILD patients. Furthermore, these proteins appear to predict the development of SSc-ILD and subsequent FVC decline, in the short-term as well [85–94]. It is important to highlight that the definition of "short-term" ILD progression is herein defined as progression within 12 months, which reflects the duration of clinical trials in SSc-ILD.

CCL18 serum levels predicted SSc-ILD progression in one study [86]. These results were, subsequently, confirmed in a second independent cohort of SSc patients, with a different, lower cut- off value of CCL18 [87]. However, these differences in cut-off levels highlight the need of standardization of CCL18 assays, before its use as a biomarker in clinical practice [88]. Furthermore, increased serum KL-6 was identified as an independent predictor of subsequent FVC decline [89–91] and associated with ILD activity [92]. Finally, increased serum SP-D, was a significant predictor of FVC decline [92,94].

5.3. The DETECT algorithm is useful to identify SSc patients at higher risk for PAH who should undergo RHC. LoE 2a

In a large, multicentre, cross-sectional, study, the DETECT algorithm, a composite biomarker which uses clinical variables, pulmonary functional tests, immunological, biological, electrocardiographic and echocardiographic parameters, proved to be a useful tool, to identify patients who are more likely to have PAH, especially those who are asymptomatic. A positive score justifies performing right heart catheterization for confirmation of PAH [95]. Subsequent work, by different research groups in different cohorts of patients with SSc, confirmed the validity of this composite biomarker as an excellent screening method due to its high sensitivity and predictive negative value, minimizing missed diagnosis of PAH [96,97], also comparing it with European Society of Cardiology/European Respiratory Society (ESC/ERS 2009) guidelines [98]. Nonetheless, it should be kept in mind that the DETECT score was developed for SSc patients with low DLCO and disease duration > 3 years and is therefore validated in this particular patient group.

5.4. High levels of plasma CXCL4 may predict development of PAH in SSc patients. LoE 2b

CXCL4 is a pro-inflammatory chemokine that regulates immune cells, such as T cells, monocytes, dendritic cells, as well as non-immune cells like endothelial cells, and may have an important role in inflammation and wound repair [99,100]. Recently, a proteome-wide analysis has demonstrated that CXCL4 is the predominant protein produced by SSc-derived plasmacytoid dendritic cells and it was identified as a potential biomarker associated with multiple organ involvement in SSc. Elevated plasma levels of CXCL4 strongly correlated with the extent of skin and lung fibrosis, as well as with early PAH development [101]. Despite the high LoE and GoR of the study, to date, no additional study has confirmed these data.

5.5. High levels of serum Anti-AT1R and Anti-ETAR antibodies may predict development of PAH in SSc. LoE 2b

Autoantibodies against the angiotensin II type 1 receptor (AT1R) and the endothelin-1 type A receptor (ETAR) have been shown to be elevated in the sera of most SSc patients, and associated with vascular and fibrotic SSc complications [102,103]. In particular, both anti-AT1R and anti-ETAR antibodies are predictive and prognostic markers of SSc-PAH [104].

6. SLE working group

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease where treatment is usually long-term or even life-long. One of the most controversial aspects of the management of SLE lies in the need to define a treat-to-target strategy, developed under the influence of evidence, to tailor to individual patients [105]. Even if to date a generally accepted definition of remission is lacking, in recent years several studies have shown that remission is a pursued and reachable target in SLE that positively impact disease outcomes halting accrual of organ damage [106–108]. The disease management during remission is an outstanding unmet need in SLE and EULAR task force suggested that is not recommended to escalate the treatment in clinically asymptomatic patients solely on stable or persistent serological activity [105].

Despite significant advances in pathogenic knowledge and therapy, SLE is still burdened by significant morbidity and mortality. Epidemiological studies show that the goal of prolonged remission or low disease activity is achievable only in a part of SLE patients [106]. The majority of patients experience frequent disease flares, significant undesirable effects of treatments and irreversible organ damage accrual [109]. The development of new drugs and the use of available therapies in the framework of a treat-to-target approach might be essential to improve the long-term prognosis of the disease [105]. Belimumab, a monoclonal antibody directed against the B-cell activating factor (BAFF) [110], is the first drug approved for the treatment of SLE. Randomized clinical trials and real-life studies demonstrated the efficacy of Belimumab in reducing disease activity and flares, sparing glucocorticoids, improving fatigue and health related quality of life and in preventing damage accrual [111,112]. However, literature data and daily life clinical practice clearly demonstrated that only a part of SLE patients adequately responds to Belimumab [113]. The identification of drug response biomarkers could be crucial to optimize the use of Belimumab in SLE.

6.1. There is no evidence that a negative serology predicts a successful withdrawal of therapy in SLE patients (with or without nephritis) in clinical remission. LoE 5

Although the topic concerning treatment withdrawal is a priority aspect in the management of patients with SLE, the currently available data on this topic are still very fragmented. Reviewing the existing literature, it has not been possible to find studies that answer directly to our research questions reformulated according to the PICO methodology, nor to identify trials designed for evaluating treatment withdrawal in inactive SLE patients with negative serology. No data are available to suggest the optimal duration of treatment in responsive patients and a possible tapering strategy [114]. Threes studies, nevertheless, focused on SLE in complete remission (including inactive SLE with negative serology) without therapy (with or without antimalarials) [106,108,115].

In the study by Urowitz et al., prolonged remission was defined as a 5-year consecutive period of no disease activity (SLE disease activity index, SLEDAI = 0) and without treatment (corticosteroids, antimalarials, or immunosuppressants). Out of 703 patients, only 12 patients (1.7%) had prolonged complete remission of at least 5 years with no treatment [115]. Zen et al. defined remission as prolonged when

lasting ≥5 consecutive years. The complete remission corresponded to the absence of disease activity (SLEDAI-2000 =0) in corticosteroid-free and immunosuppressant-free patients. During the 5-year follow-up, 16 patients (7.1%) achieved prolonged complete remission [106]. Medina-Quiñones et al. studied lupus patients achieving a complete remission, without clinical or serologic features and no treatment with steroids and immunosuppressive drugs for at least 3 years. Overall 77 patients (14.5%) achieved complete remission for at least 3 years [108].

6.2. In lupus nephritis, negative serology does not predict a successful withdrawal of therapy. LoE 3b

Regarding lupus nephritis, only one study partially covered our research question. Moroni et al. reported their cumulative experience with treatment withdrawal in patients with biopsy-proven lupus nephritis with a follow-up of at least 5 years [116]. The authors completely stopped treatment in 52 of 161 (32 %) patients with class III, IV or V lupus nephritis. The decision of interrupting therapy was taken for those patients who had achieved a stable clinical remission and did not show any renal or extra-renal flare. Of 52 patients who stopped therapy, 32 (61.5 %) never developed new flares and continued without any therapy for the subsequent 101.8 months (range 44–180 months) of observation after interruption of treatment. The other 20 patients (38 %) had at least one flare. No difference in the prevalence of hypocomplementemia and anti-dsDNA antibodies was observed among patients with and without flares [116].

The therapeutic scheme to be adopted in lupus nephritis during complete remission, when and how to reduce corticosteroids and immunosuppressants are unanswered questions, as well as it is not clear the role of serology in spacing/tapering strategy [117]. Recently a position paper has specifically addressed this point [118]. The experts have emphasized that the essential prerequisite for a safe withdraw of therapy is patient's remission. The authors have remembered that special attention must be given to tapering slowly, progressively and under strict medical surveillance for avoiding severe or irreversible renal failure after an abrupt discontinuation [118].

6.3. Available data demonstrated that baseline BAFF serum levels do not predict response to Belimumab in SLE patients. Other baseline biomarkers, such as high dose of glucocorticoids, low complement fragment C3 or C4, positivity to anti-dsDNA, might be useful in predicting response to Belimumab. LoE 1b

Wallance et al. reported the results of the phase II randomized clinical trial on the use of Belimumab in addition to standard of care (SOC) in 449 active SLE patients [119]. Considering the serologically active subgroup (ANA titer > 1:80 and/or anti-dsDNA > 30 IU/ml), a significant greater proportion of patients treated with Belimumab reached the SLE Responder Index (SRI) compared to placebo (46% versus 29%). In the exploratory subgroup analysis, the mean percent change in SELENA-SLEDAI from baseline to week 52 was compared after stratification of patients according several biomarkers. A significant reduction in SELENA-SLEDAI was observed in patients treated with daily dose of prednisone ≥ 7.5 mg, in seropositive patients, in patients positive for ANA or anti-dsDNA or with low complement fragment components C3 or C4. Nevertheless, the reduction of SELENA-SLEDAI in patients with serum BAFF above the limit of detection compared with patients with undetectable BAFF did not reach the statistical significance [119]. Roth et al. performed a post hoc analysis of pooled data from phase III clinical trials BLISS-52 and BLISS-76. In the efficacy analysis, 1108 SLE patients were stratified according to baseline BAFF serum levels (≥ 2 ng/ml verus < 2 ng/ml). In both subgroups (high and low basal BAFF) about half of patients achieved the reduction of SELENA-SLEDAI of almost 4 points and the SRI response at week 52 [120]. Moreover, in both subgroups, the study outcomes were reached in the first 24 weeks and approximately maintained over time. The post-hoc analysis did not provide a direct statistical comparison of subgroups. However, numerically greater differences in study outcomes for Belimumab treated patients versus placebo were reported in the groups with high basal BAFF compared to the low basal BAFF group [120].

7. APS working group

Antiphospholipid syndrome (APS) is an autoimmune disease clinically characterized by vascular thrombosis and pregnancy morbidity. Diagnosis is confirmed by the persistent presence of anti-phospholipid antibodies (aPL) in patients' plasma [121]. At present, three aPL assays are included in the classification criteria: Lupus Anticoagulant (LA), anticardiolipin (aCL) antibodies and anti-β2glycoprotein I (anti-β2GPI) antibodies of IgG and/or IgM isotype [122]. In the last decade, a number of new tests, with variable sensibility and specificity, have been proposed as additional serological biomarkers of APS. Among them, anti-phosphatidylserine/prothrombin (anti-PS/PT) antibodies and epitope specific anti-beta2GPI antibodies have been suggested to display higher diagnostic and prognostic value for APS [123]. As a matter of fact, β2GPI and pro-thrombin have been addresses as the most important antigenic targets of aPL [123].

7.1. Anti-β2GPI antibodies

β2GPI is a positively charged glycoprotein composed by 5 domains. Several studies have shown that anti-β2GPI autoantibodies can be directed against different domains, even if domain I (D1) has been identified as the immune-dominant epitope in APS [124]. Moreover, this subpopulation of autoantibodies has been demonstrated to play a pathogenic role in APS [125–127]. On the contrary, antibodies targeting the fourth and fifth domain (D4/5) of the molecule have been identified in aPL asymptomatic carriers and in patients with infectious diseases, atopic dermatitis and babies born from patients with autoimmune diseases [128,129]. To assess the diagnostic and prognostic value of epitope specific anti-beta2GPI antibodies, a systematic review of the literature, from July 2007 to July 2017, including randomized clinical studies, observational studies and reviews and on APS, has been performed. Of the 25 potentially relevant publications, 15 studies have been selected for analysis. Pulling together the results of 11 papers, for a total of 1585 patients, the overall estimated median prevalence of anti-D1 antibodies was 43%, ranging from 26.7% in SLE patients to 55.4% in primary APS [130].

7.1.1. The addition of anti-domain I to laboratory classification criteria seems to increase the risk of thrombosis. LoE5

Several different studies have shown a significant association of anti-D1 positivity to the risk of thrombosis, while the correlation with pregnancy morbidity was less evident [130–134]. Interestingly, anti-D1 positivity has been associated to triple aPL positivity, LA positivity and the presence of an additional autoimmune disease and higher anti-D1 titers have been observed in triple aPL positive APS patients and in patients with a history of thrombosis [130–134]. By contrast, only 3 studies reported the prevalence and clinical significance of anti-D4/5 autoantibodies. All these papers show that anti-D4/5 are more prevalent in asymptomatic aPL positive subjects [128,129,135].

7.1.2. There is no evidence that anti-domain I can substitute anti-beta2GPI I. LoE5

Even if anti-D1 positivity has been clearly associated with the risk of thrombosis, a relevant prognostic value of this subgroup of autoantibodies for pregnancy complications is still to be confirmed [130–134]. In several different studies, anti-2GPI antibodies has been shown to display a higher prognostic value than anti-D1 for thrombotic events [131,136,137]. Moreover, Andreoli et al. have reported that a small but relevant proportion of APS patients can display anti-2GPI

positivity even if they do not react with domain 1 [129]. At present, anti-domain I can be considered an additional, rather than an alternative, prognostic marker of APS.

7.2. Anti-PS/PT antibodies

Among new serological biomarkers of APS, antibodies specific to phospholipid-binding plasma proteins, phospholipid–protein complexes, and anionic phospholipids other than cardiolipin (including phosphatidylserine, phosphatidylinositol and phosphatidic acid). Antibodies against human prothrombin (aPT) and the complex of prothrombin bound phosphatidylserine (aPS/PT) have been strongly associated to the APS, even if their clinical relevance and diagnostic utility remain to be fully elucidated [138]. Although, it seems that aPT and aPS/PT belong to different autoantibodies families, they can both be present in the same patient [138–143].

7.2.1. The presence of anti-PS/PT seems to increase the risk of clinical manifestations of APS. LoE5

Current evidence suggest that aPS/PT measurement could help in the evaluation possible adverse pregnancy outcomes and thrombosis in patients suspected of suffering from APS and the assessment of thrombotic risk in patients with previous thrombosis and/or Systemic Lupus Erythematosus (SLE) [138,139]. A systematic review of Sciascia S, et al. reported an increased risk of thrombosis associated to aPT and aPS/PT (OR 2.3 [95%CI 1.72–3.5]) [139]. Moreover, aPS/PT seemed to be a stronger risk factor for thrombosis, both arterial and/or venous than aPT (OR 5.11 [95%CI 4.2–6.3] and OR 1.82 [95%CI 1.44–2.75], respectively). However, these promising associations are based on the results of 10 studies, almost all but one, retrospective reports [138]. Recently, the accuracy of IgG aPS/PT for APS diagnosis in heterogeneous population has been confirmed in a large multicenter study, reporting a higher prevalence of aPS/PT IgG in APS patients than in those without (47% versus 12%), with an OR of 6.4. In this study, sensitivity, specificity, LR + and LR- for APS diagnosis were 47%, 88%, 3.9 and 0.6, respectively [140]. Moreover, Hoxha et al. showed a positive association between IgM aPS/PT titres and both vascular thrombosis and pregnancy morbidity. Additionally, IgG aPS/PT was significantly associated with venous thrombosis [142].

7.2.2. The presence of anti-PS/PT seems to identify very few patients with the so called seronegative APS. LoE5

The concept of the so called seronegative APS (SNAPS) was introduced in 2003 to identify patients with highly suggestive manifestations of APS, but persistently negative for the classification laboratory criteria [144]. In the past 5 years, research has been focused on the identification of “new” aPL, not included in the serological criteria, in seronegative APS patients (3,20,22). Few studies have reported a relevant prevalence of anti-PS/PT antibodies in SNAPS patients. Amengual et al found an IgG aPS/PT antibody positivity in 6% of 17 patients with clinical manifestations of APS but negative for the classification laboratory criteria [141]. More recently, Shi et al, showed that 51% of patients with SNAPS had IgG and/or IgM anti-PS/PT antibodies and that the prevalence of anti-PS/PT was significantly higher in SNAPS patients compared to SLE patients [145].

Taking together these findings, anti-D1 and anti-PS/PT antibodies can currently be addressed as potential additional serological biomarkers of APS, that can help for a better stratification of thrombotic and obstetric risk in APS, in combination with the classification APS laboratory markers. More prospective clinical studies are needed in order to define the specific role of aPS/PT as a potential biomarker of APS diagnosis.

8. pSS working group

pSS is an autoimmune disease characterized by an inflammatory infiltrate affecting the exocrine glands, mainly the salivary and lacrimal glands, which may lead to a decrease in the glandular function. [146]. The main symptoms include dryness of the mouth and eyes. Some extraglandular features may be observed, such as vasculitis, interstitial lung disease, interstitial nephritis or severe cryoglobulinaemic vasculitis and central nervous system involvement [147]. Furthermore, a significant percentage of pSS patients may develop B cell lymphoma [148]. Given the clinical heterogeneity and outcome of these patients, due to the different involvement observed in target organs, an early identification of the patient’s subsets, particularly for the subgroup of patients prone to lymphoma development remains a major challenge [149]. So far, there is a strong need for new predictive clinical or biologic biomarkers, which could, at baseline, identify those patients with a poor outcome, and drive the best optimal therapeutic intervention, tailored to the clinical phenotype of the patients. Possible predictive biomarkers of unfavourable outcomes in pSS include serum CXCL13 and BAFF levels, and the presence of germinal centre (GC)-like structures in minor salivary gland (MSG) tissue. CXCL13 is a chemokine involved in the formation and maintenance of GC-like structures in autoimmune diseases [150]. Data suggest it may function as a biomarker of GC formation following vaccination for example [151]. BAFF is essential for B cell survival and GC maintenance [152,153]. Different studies reported higher levels of serum CXCL13 and BAFF in pSS patients who developed lymphoma [154,155]. GC-like structures in MSG biopsies are associated with more severe disease and with the presence of autoantibodies and their presence and function in MSG may be associated with the lymphoma risk [156]. At present, there is a general consensus in available literature that in pSS patients low C4, cryoglobulins, purpura, vasculitis and parotid swelling are strongly associated with lymphoma development [148, 157].

8.1. The predictive value of CXCL13 in pSS, for both poor prognosis and therapeutic response, remains to be clarified. LoE 2b

CXCL13 is overexpressed in different chronic inflammatory diseases and is part of lymphoid tissue neogenesis, notably in the segregation of T and B cells into the T-cell zone and B-cell follicles [150]. In pSS salivary glands CXCL13 may directly control the formation and maintenance of functional ELSs and may promote, in a subset of patients the progressive development to lymphoma. CXCL13 levels significantly correlate with ESSDAI and, CXCL13 serum levels are significantly higher in pSS patients with an active disease (ESSDAI $\geq$ 5) [150,154]. In a Japanese cohort of 88 pSS patients CXCL13 serum levels correlate with lymphadenopathy, glandular, pulmonary and biologic domains. Furthermore, the Authors found a correlation between CXCL13 serum levels and hypergammaglobulinemia, underlying the possible correlation between the biomolecular status of salivary gland pathology and lymphomagenesis [158]. Furthermore, increased CXCL13 serum levels have been shown in pSS patients with the highest levels observed in patients with lymphoma [154]. Interestingly, the baseline CXCL13 levels of those patients who developed lymphoma during follow-up, were higher than the levels observed in patients who did not develop lymphoma [154]. These data should be confirmed in larger studies. In a small open label study of abatacept in pSS, reduction on CXCL13 levels correlated with reduction in ESSDAI scores [159], but this requires confirmation in larger, randomised controlled trials.

8.2. The predictive value of baseline BAFF levels for lymphoma development and therapeutic response to RTX should be further assessed. LoE 2b

BAFF levels are critical for peripheral B cell survival and differentiation, GC-like structure formation, plasma cell survival and IgG and IgE class switching. Due to these activities, BAFF may play a crucial role in pSS pathogenesis and in GC formation [160]. In fact, different studies show a correlation between BAFF serum levels and ESSDAI scores, especially for lymphadenopathy, glandular and pulmonary domains

[155,158]. Furthermore, BAFF serum levels are higher in pSS patients with lymphoma and, in this setting, increased BAFF levels at diagnosis, are significantly associated with lymphoma development, as confirmed by multivariate analysis [154]. Increased BAFF serum levels also seem to be predictive of rituximab (RTX) treatment failure, suggesting a possible predictive role of BAFF serum levels in identifying a subset of patients suitable to be treated with this B-cell depleting agent [161]. On the contrary, data from a small open label study suggest that serum BAFF levels are not predictive of clinical response [162]. Although these results look very promising for personalized medicine, they have to be confirmed in larger cohorts before being helpful in daily clinical setting.

8.3. The clinical utility of the presence of GC-like structures, in MSGs, to predict lymphoma development should be further assessed with standardization of technique and multicentre studies given the relatively low incidence of lymphoma. LoE 3b

It has been shown that approximately 25% of pSS patients display GC-like structures in their salivary glands, and these patients have more severe disease in terms of higher salivary gland focus score, higher prevalence of rheumatoid factor, anti-SSA, and anti-SSB antibodies [163]. Approximately 5% of patients with pSS will develop non-Hodgkin B-cell lymphomas of mucosal-associated lymphoid tissue, commonly in the parotid glands. Different reports describe the association between GC-like structures and lymphoma development, highlighting that the detection of GC-like structures, by H&E staining, may be a highly predictive and an easy-to-obtain marker for lymphoma development [156]. Two different retrospective small cohort studies showed that the development of lymphoma in pSS patients was associated with the presence of GC-like structures in MSG biopsies at the time of diagnosis [163,164]. Another observational retrospective study did not find a strong association with lymphoma development but confirmed that GC-like structures in MSGs were associated with the presence of systemic manifestations [165]. The absence of GC-like structures in MSGs has been associated with a high negative predictive value for lymphoma [163]. However not all studies have confirmed an association of GC-like structures and lymphoma development [166,167] and the majority of studies investigating this relationship have issues of study design, being generally retrospective studies, with small populations of patients, and using different methods of case identification.

The identification of the GC-like structures should ideally be confirmed by IHC in order to identify the degree of organisation. In fact, some IHC studies, have failed to confirm the presence of GC-like structures observed by H&E [156]. Further work to standardise markers to be used is required however due to the potential importance of this topic [168], a strong scientific agreement should be reached regarding the appropriate procedures to draw a definitive conclusion.

9. Discussion

This work derived from a systematic review of available literature and International Experts' Consensus may provide a comprehensive highlight of the role of biomarkers in management of patients affected by autoimmune rheumatic diseases treated by conventional and/or biological therapies (Table 1). The main objective of this work would be to counsel physicians on the suitable way to address the possible role of mechanistic, clinical and therapeutic markers in this context. Our paper synthesises key points and new information, largely from recent or ongoing medical research derived from technical review, that may have implications for management of these patients [169].

The continued identification of new biomarkers specific to autoimmune rheumatic disease is crucial for translation into personalised medicine, in terms of patient management. In fact, the personalised medicine is an emerging practice of medicine that uses the patients' phenotype to guide decisions made in regard to the diagnosis, prevention and treatment of diseases [170-174]. Biomarkers profiling may be useful for tailoring the right therapeutic strategy for the right patient at the right time, and/or to onset of a specific complications [175,176].

Despite providing a comprehensive synthesis of the current available literature, this review is impaired from major limitations and, therefore, all the results should be cautiously interpreted. The main limitation is related to the poor methodological quality of a vast percentage of the included studies, mainly observational studies providing less reliable findings when compared with possible randomised controlled trials primarily and specifically designed. On these bases, it could be difficult to perform comparisons between extracted data and future specific designed studies are needed to entirely clarify these features. On the other side, it must be pointed out that autoimmune diseases are rare diseases and organising specific designed studies to investigate the role of biomarkers may be a challenge. In addition, our consensus statements do not provide specific algorithms or guidelines for practice because these depend on different variables, such as cost, expertise and practice circumstances.

In conclusion, the results derived from our systematic review and International Experts' Consensus confirmed that the better understanding and targeting of existing therapies is still an important field of research. Biomarkers and personalised medicine would represent the key points in the future management of patients affected by autoimmune rheumatic diseases.

Competing interest

None
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