The growing role of precision medicine for the treatment of autoimmune diseases; results of a systematic review of literature and Experts' Consensus

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Abstract

Autoimmune diseases (AIDs) share similar serological, clinical, and radiological findings, but, behind these common features, there are different pathogenic mechanisms, immune cells dysfunctions, and targeted organs. In this context, multiple lines of evidence suggest the application of precision medicine principles to AIDs to reduce the treatment failure.

Precision medicine refers to the tailoring of therapeutic strategies to the individual characteristics of each patient, thus it could be a new approach for management of AIDS which considers individual variability in genes, environmental exposure, and lifestyle. Precision medicine would also assist physicians in choosing the right treatment, the best timing of administration, consequently trying to maximize drug efficacy, and, possibly, reducing adverse events.

In this work, the growing body of evidence is summarized regarding the predictive factors for drug response in patients with AIDs, applying the precision medicine principles to provide high-quality evidence for therapeutic opportunities in improving the management of these patients.

Key words

Precision medicine; rheumatoid arthritis; spondyloarthritides; systemic lupus erythematosus; antiphospholipid syndrome; primary Sjögren's syndrome; systemic sclerosis.

1. Introduction

Autoimmune diseases (AIDs) are a large group of different conditions associated with immune system dysfunction and aberrant immune response [1]. AIDs share similar serological, clinical, and radiological findings. However, behind the common tracts, AIDs hidden different pathogenic mechanisms, immune cells dysfunctions, and targeted organs [2]. Despite all these differences, usually, AIDs patients are treated with a limited number of immunosuppressants, sometimes with partial evidence or transferring physicians' knowledge from an AID to another one [3]. In fact, several clinical trials failed in reaching their primary endpoints in AIDs and these results could be linked to the unmasked molecular heterogeneity among the patients, in spite of similar clinical features [1, 4].

In this context, multiple lines of evidence suggest the usefulness of application of precisions medicine (PM) principles to AIDs. PM has been defined as a new approach for disease treatment and prevention that considers individual variability in genes, environmental exposure, and lifestyle [5]. PM main goal is to tailor the treatment strategy according to patient characteristics and to help physician in choosing the right treatment and the better timing of administration, thus trying to maximize the efficacy, and, possibly, reducing the adverse events (AEs). PM considers genetic factors, age, nutrition, health status, environmental exposure, and concurrent therapies to predict the response of a patient to a specific drug [6]. The ultimate PM purpose is to link patient phenotypes to targeted therapies and to bring back therapeutic choice to an individual scale [3]. More importantly, the availability of novel drugs with newer and newer mechanisms of action, and innovative therapeutic strategies, may highlight even more the issue to early identify patients who could better respond to a drug than another one [7,8].

In this work, the growing body of evidence is summarized regarding the predictive factors for drug response in patients with AIDs, applying the precision medicine principles to provide high-quality evidence for therapeutic opportunities in improving the management of these patients.

2. Materials and methods

2.1. Aims of the project

The overarching aim of the workshop "The precision medicine in profiling the patients regarding therapy. From Pathology to treatment, what evidence in rheumatic and autoimmune diseases?" was to apply the PM principles in the therapeutic strategy selection in

patients with AIDs. The general methodology relied on a Delphi Technique forecast aimed at producing, starting from the results of a systematic review of available literature (SRL), a set of statements summarising the consensus among the Experts, as previously reported [9, 10]. The SRL was part of an International project named "The precision medicine in profiling the patients regarding therapy. From Pathology to treatment, what evidence in rheumatic and autoimmune diseases?" aimed to synthetize PM-based features in the management of patients with AIDs. A Scientific International Committee, composed by a group of Experts and bibliographic Fellows, was identified and choose some relevant clinical questions on PM in AIDs treatment, needing further and updated clarifications according to available scientific evidence and joined Experts' opinion. The Experts were selected based on their individuals' contributions to the specific fields included in the topics of the meeting. Six AIDs were evaluated: rheumatoid arthritis (RA), spondyloarthritides (SpA), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), primary Sjogren's syndrome (pSS), and systemic sclerosis (SSc). Selected 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 4-5, 2019.

2.2. Search design and strategy

For each one of these 6 topics, the SRL was performed in indexed international Journals (Medline via Pubmed, Scopus, and Cochrane database). The Scientific Committee agreed to analyse the literature from July 1, 2009 – July 1, 2019. The search strategy combined indexed and free-text terms, interventions, and outcomes of interest in Medline via Pubmed, Scopus, and Cochrane database, as requested for each topic. PICO strategy served as rephrasing strategy across working groups, along with pre-defined "Population", "Intervention", "Comparison", "Outcomes", as requested by each topic research question. The main search was thus formulated using a string of relevant terms. The main keywords were used in different combinations in order to improve the accuracy of the search strategy. The bibliography of relevant articles was also hand-searched for the identification of other potentially suitable studies. Included studies were full-text manuscripts in the English

language conducted in adult patients with AIDs. To be included in the final analysis, studies had to report data concerning population, intervention, comparison, and outcomes were requested for each single selected topic. Narrative reviews, editorials, scientific conference abstracts, case reports, and preclinical studies were excluded. Papers retrieved by literature search but reporting insufficient data according to the selected PICO strategy were also excluded. The levels of evidence, suggested by Oxford University, were followed to identify the hierarchy of study types (http://www.cebm.net/oxford-centre-evidencebased-medicine-levels-evidence-march-2009/).

2.3. Study identification and data extraction

In each working group, full-text articles were screened and selected after analysing titles and abstracts by bibliographic Fellows, then independently verified by corresponding senior Reviewers. After the screening phase, the bibliographic Fellows independently evaluated the selected abstracts and the related full texts to determine their inclusion according to the eligibility criteria. Any uncertainties and/or disagreements were resolved by discussion until reaching a final consensus. Bibliographic fellows independently performed data extraction. Corresponding senior reviewers verified the process. After that, the results of the analysis of the literature were summarized, presented, and further inputs were obtained in expanded working groups, including other authors. Conflicting results were further analysed by discussion, considering the 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. Disagreements were resolved by discussion until reaching a final consensus. In the subsequent plenary session, the statements were 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 wording for clarity or addressing redundancies were considered, while any change to the meaning was not accepted.

3. RA working group

3.1 Do inflammatory markers predict the response to IL-6 inhibitors?

3.1.1 There is no association between inflammatory markers at baseline (CRP, ESR) and attainment of response when using composite measures that include CRP and/or ESR e.g. DAS28 remission or EULAR response, following tocilizumab treatment in RA (LoE 2b).

Interleukin (IL)-6 is one of the many cytokines, which is involved in the pathophysiology of RA [11]. One of its pleiotropic effects is to increase the production of acute phase reactants by hepatocytes [12]. Accordingly [13], IL-6 inhibitors, which have been proven effective for the treatment of RA in several studies, have an important suppressive effect on inflammatory markers [14].

We identified 8 research articles that specifically evaluated if inflammatory markers could predict a response to tocilizumab (TCZ) [13, 15-21] and none for other IL-6 inhibitors. Five were observational studies [13, 15, 19-21] and 3 post-hoc analysis of randomised controlled trials (RCTs) [16-18]. None of the post-hoc RCTs analyses found an association between baseline levels of inflammatory markers and response. In particular, a pooled analysis of 5 RCTs including 4,186 participants did not find any associations between baseline CRP levels and DAS28 at 24 weeks. In the observational studies, one study found an association with levels of CRP > 10 mg/l at baseline and higher EULAR response but not with higher rates of DAS28 remission at 24 weeks [13]. Another study found that ESR>30 mm/h and CRP>10 mg/dl were associated with higher odds of achieving DAS28 remission at 3 months but not 6 months [19]. The three other studies did not find any association between inflammatory markers and treatment response. However, most of the studies had a small sample size and were of low quality. All of them except one [18] used univariate selection of covariates [13, 15, 19-21] and/or stepwise selection [13, 15, 19-20] for their regression models, which should be avoided to select covariates in prediction modelling [22-24]. Some did not present the number of outcome events [18, 21] or did not control for other covariates [16-17]. One study did not describe the baseline population [16] and most did not explain how they handled missing data [13, 15, 16, 21]. None of the studies explained if the assumptions of the models they used were satisfied. In addition, all RCTs studies needed moderate to severe active RA as inclusion criteria, which includes high levels of CRP. Therefore, baseline levels of inflammatory markers may not have been different enough between participants to allow for the analysis of their predictive values on response. Furthermore, all the studies used DAS28 or EULAR-response (improvement of DAS28) as one of their main outcomes. Only 3 small studies used another disease activity outcome (CDAI/SDAI remission, Boolean remission or >20% decrease in TJC/SJC) [13, 17, 21]. Four of the studies presented in their results the important influence of TCZ on the decrease of inflammatory markers, which is a significant component of DAS28 [13, 15-17]. Considering the major effect of IL-6 inhibitors on DAS28 and the inclusion of the studied predictive covariates in the score, using it as an outcome may

not be appropriate [14, 25] and may explain why the levels of inflammatory markers at baseline were not found predictive of the response to TCZ in these studies.

3.1.2 Higher levels of CRP are associated with lower tocilizumab discontinuation in RA (LoE 4).

One prospective observational study looked specifically at the association of levels of inflammatory markers and TCZ retention [20]. In this study, in a categorised stratified analysis by quartile of CRP, higher quartiles of levels of CRP at baseline were associated with lower discontinuation. This effect persisted in the multivariate analysis, where higher levels of CRP at baseline, used as a continuous variable, was also predictive of lower discontinuation.

3.2 Could the presence of metabolic comorbidities (obesity and diabetes) influence the response to biologic DMARDs?

3.2.1 In RA, obesity does not appear to influence response rates (good EULAR response and drug retention rate) to both abatacept (LoE 2b) and tocilizumab (LoE 4). On the contrary, obesity seems to impair the response with TNFis (LoE 3b). Conflicting data are available on rituximab (LoE 4).

Overweight and obesity are defined as an abnormal or excessive fat accumulation [26] which are usually assessed by body mass index (BMI). High BMI is common among patients with RA with over 60% being overweight or obese [27, 28], and it is associated with higher disease activity and disability [29, 30]. On these bases, a systematic review of literature was performed to assess whether obesity could influence the efficacy of biologic DMARDs, and 17 manuscripts were retrieved investigating this issue. Seven studies evaluated the impact of obesity on clinical response to abatacept. In a 6-month post hoc analysis of a 2-year prospective study [31], the influence of baseline BMI was investigated on efficacy and retention rate of intravenous abatacept (ABA) in 643 patients. After 6 months, there were no significant differences, according to BMI groups, in achieving a good/moderate EULAR response (80.7, 86.1 and 77.0% for underweight/normal, overweight and obese groups, respectively) and on overall retention rate (89, 92 and 89% for underweight/normal, overweight and obese groups, respectively) [31]. Similar results were observed in a post-hoc analysis of ACQUIRE trial [32], involving 1456 patients, treated with either subcutaneous or intravenous ABA. After 6 months, no significant differences in percentages of remission were reported across BMI groups and different routes of administration (27.3, 20.0%, and 25.4% for underweight/normal, overweight and obese groups treated with subcutaneous ABA, respectively; 25.0, 30.0, and 18.5% for underweight/normal, overweight and obese groups treated with intravenous ABA, respectively) [32]. In addition, pooled data of 10 prospective

cohorts, involving 2015 patients treated with intravenous ABA, showed that 2-year drug retention rate of intravenous ABA did not seem to be decreased by obesity (52.8, 51.8, 48.3, and 55.2% for under-/normal weight, overweight, obesity, and severe obesity, respectively) [33]. Although of interest, it must be pointed out that these data are derived by sponsored studies, which are characterised by some limitations when compared with academic ones [34]. The other studies retrieved by systematic literature review, which investigated the influence of obesity on clinical response to ABA, showed similar results [35-38]. Four studies assessed the impact of BMI on clinical response to TCZ. In a retrospective study including 200 patients [39], EULAR criteria of response were assessed according to BMI after 6 months. The authors did not report any significant association between EULAR response, remission or low disease activity with BMI, suggesting the clinical response to TCZ is not influenced by obesity [39]. In another retrospective study [35], clinical response to TCZ was stratified according to BMI. In 115 patients, BMI did not differ in groups of responders or not responders and, similarly, stratifying results on clinical response according to BMI, non-significant differences were retrieved after 6 months (68, 73, and 80% for normal, overweight, and obese patients, respectively) [35]. Additional retrospective studies, on a small number of patients, paralleled these results [36, 37]. The SRL also retrieved 8 studies investigating the influence of obesity on efficacy of TNFis. In a prospective study [40], the authors assessed the impact of baseline BMI on clinical response to infliximab on 89 patients. After 16 weeks, a lower percentage of obese patients achieved a good response (84, 75, and 50% for normal, overweight, and obese patients, respectively) and, similarly, non-responder patients had higher value of BMI. A negative association was also reported between BMI values and DAS28 decreases [40]. In a national registry, including 641 patients treated with TNFi [41], a low percentage of obese patients achieved the remission after 12 months (32.0 and 15.2% for non-obese and obese, respectively). Even stratifying the results for different TNFis, a low percentage of obese patients achieved the remission [41]. In other studies, evaluating this issue, a lower effectiveness of TNFis was further observed in obese patients [36, 37, 42]. Additionally, obesity lowered the chance of attaining remission, as shown in post hoc analyses of randomised clinical trials [43, 44]. Differently, only a retrospective analysis of US veterans showed that high BMI did not seem to influence the rate of TNFis discontinuation [45]. Finally, conflicting results are reported in 2 studies assessing the impact of obesity on clinical response to rituximab (RTX) [37, 46]. A retrospective study described the influence of obesity on effectiveness in 58 patients treated with RTX [37]. A lower percentage of obese patients

reached the remission after 12 months (33 and 7% for normal and obese, respectively) [37]. Another retrospective study evaluated the effectiveness of RTX according to BMI in 114 patients [46]. BMI was non-different among patients with EULAR good response and, similarly, the clinical response was not different across categories of BMI after 6 months (23.7 and 21.1%, for non-obese and obese, respectively) [46].

3.2.1 Anakinra appears to have a bidirectional efficacy, on both glycaemic and inflammatory parameters, in patients with RA and comorbid T2D (LoE 2b).

A consistent connection between RA and glucose derangement has increasingly been reported, as suggested by occurrence of type 2 diabetes (T2D) in these patients, thus contributing to excessive cardiovascular burden of the disease [47]. The inflammatory pathogenic pathway in T2D has recently suggested new therapeutic targets by using biologic DMARDs licensed for RA [48, 49]. In this context, the SPL retrieved a randomised trial, which investigated whether IL-1 inhibition with anakinra (ANK), a recombinant human interleukin-1 receptor antagonist, could improve both glycaemic and inflammatory parameters in patients with RA and T2D compared with TNFis [50]. Thirty-nine patients with RA and T2D were randomised to ANK or to a TNFi. After 6 months, patients in ANK group had a significant reduction of glycated haemoglobin (HbA1c%) which was not observed in TNFi group (0.93 HbA1c% crude difference between groups). Concerning RA, a progressive reduction of disease activity was observed in both groups, although a larger percentage of ANK-treated patients reached a good EULAR clinical response [50]. Taking together these findings, IL-1 inhibition could be considered a targeted treatment for RA and T2D, since these patients reached therapeutic targets of both diseases. In fact, differently from TNFis, IL-1 inhibition could also improve insulin sensitivity and restore pancreatic regulation in RA and T2D, as additional therapeutic effect [51].

3.3 In RA patients, does the analysis of B cell lineage markers help to predict treatment response to B cell depletion with Rituximab?

3.2.1 In RA, rituximab induces a depletion of circulating B cells in all treated patients, thus the level of B cell depletion in the peripheral blood after the first infusion does not predict response (LoE 2b).

3.2.2 Highly sensitive flow cytometry and the pre-treatment analysis of specific B cell subpopulations or B cell lineage markers help to identify responders (LoE 3b). Upon treatment with RTX, a variable depletion of synovial B cells has been described and the presence of specific

B cell sub-populations in synovia, such as CD79a+ B cells and pre-plasma cells, has been associated with treatment response (LoE 4).

RTX is an established treatment for RA, as shown by several RCTs that confirmed its efficacy. RTX targets CD20+ B cells, inducing their depletion in the peripheral blood. However, pharmacodynamics and post-hoc analyses of these trials have shown that the levels of pre-treatment B cells or the depth of their depletion, as measured by conventional flow cytometry, do not associate with treatment response [52-60]. The use of highly sensitive flow cytometry might help to set a stricter cut-off level for B cell depletion; however, this has only been tested in small observational studies with somehow contradictory results [61-63]. The analysis B cell sub-populations in the peripheral blood, such as CD27+ memory B cells [64, 65] and pre-plasma cells [66]. Additionally, a number of circulating markers have been linked to the response to RTX, such as mRNA levels of IgJ [67], polymorphism of BAFF [68], Fcgamma R IIIa [69] and IL-6 [70], whole blood transcriptomic signatures [71], serum IL-33 [72] and CCL19 levels [73]. Importantly, most of these observations originate from individual studies with relatively small numbers and have not been reproduced or validated, therefore their clinical utility for patient stratification to rituximab treatment is limited.

In contrast to the complete depletion of peripheral blood B cells, a variable depletion of B cells and other immune cells in synovia following treatment with RTX has been described [74-82]. In particular, the number of pre-treatment synovial CD79a+ B cells [74, 78], pre-treatment synovial molecular signatures [81] and the reduction of synovial plasma cells [76] have been identified as factors associated with response to RTX. However, the small number of patients analysed and the use of different timepoints makes it difficult to draw conclusions on the association of synovial B cell signatures with treatment response to RTX.

4. Spondyloarthritides working group

4.1 In SpA patients, could HLAB27, HLACw6 and ERAP1 represent genetic biomarkers able to predict treatment response to csDMARDs and bDMARDs (TNFis, IL17is, IL12/IL23is)?

4.1.1 No work addressed the potential role of HLACw6 and ERAP1 in prediction of treatment response to csDMARDs and bDMARDs in SpA patients. More data were available on HLAB27 status in predicting therapeutic response in SpA and these were moderately useful for personalization of therapy in the clinical setting (LoE 2b).

The spondyloarthritis (SpA) complex includes a group of inflammatory arthropathies with peculiar clinical manifestations including axial involvement, sacroiliitis, peripheral arthritis,

enthesitis, and dactylitis. Extra-articular involvement, such as uveitis, colitis, psoriasis or other cutaneous manifestations can also occur frequently [83,84]. SpA spectrum comprises Ankylosing spondylitis (AS), non-radiographic Axial Spondyloarthritis (nr-axSpA) Psoriatic arthritis (PsA), Reactive arthritis (ReA), Arthritis related to Inflammatory Bowel Diseases, and forms that do not satisfy recognized criteria for these definite entities, defined as Undifferentiated SpA (uSpA) [85]. Etiopathogenetic mechanisms underlining SpA remain still unclarified. The most accredited hypothesis provides a complex interaction between genetic susceptibility and environmental factors, leading to immunological dysregulation [83]. In the last decades, an increasing attention has been paid to SpA early diagnosis and therapy initiation. Such factors, as age and disease duration appear to influence the response to therapies [83]. To date, recognition and better definition of SpA specific biomarkers could be relevant for diagnostic and prognostic purposes in the view of a more tailored and personalized approach [86] The identification of genetic, histologic, and clinical predictors of response to different biological disease-modifying anti-rheumatic drugs (bDMARDs) could help clinicians to make evidence-based decisions in order to maximize benefits from treatment and personalize the appropriate therapeutic strategy. In addition, this approach could also improve the cost/benefit and benefit/risk ratios in patients starting treatment with cs- and bDMARDs [87].

HLA-B*27 represents a key susceptibility gene for SpA pathogenesis and endoplasmic reticulum aminopeptidases (ERAP) have been associated with alterations in the antigenic pool expressed by HLA-B*27 molecules [88]. Further, HLA-Cw6 allele has been also associated with cutaneous involvement in PsA patients [89]. Among the most significative findings, recent studies showed that HLA-B27 positivity represented a consistent and strong baseline predictor of remission among patients with active SpA receiving TNF inhibitors (TNFis) [90-93]. In a pooled analysis from four large clinical trials, treatment response under TNFis at 12 weeks was greatest among patients with AS duration ≤ 2 years and even more pronounced in subgroups of young pts HLA-B*27-positive [94]. In a study in which anti-TNF therapy was associated with significant clinical/functional improvement of patients with nr-axSpA, over 24 weeks, number of HLA-B*27 positive subjects on bDMARDs was higher (28/71; 39.4%), when compared to those on PBO (11/83; 13.3%) [95].

4.2 In SpA patients, could mutations of the autoinflammatory genes MEFV, NOD 2, TNFRSF1A and NLRP 3 genes) represent genetic biomarkers able to predict treatment response to csDMARDs and bDMARDs TNFis IL-17is, IL-12 /IL-23 is)?

4.2.1 Both in PsA and axSpA, there are no data on HLA-Cw6, ERAP1, MEFV, CARD15/NOD2, TNFRSF1A, and NLRP3 as potential biomarkers for treatment response to bDMARDs (TNFis, IL17Ais, and IL12/23is) or csDMARDs. In axSpA, HLA-B27 could be considered a biomarker of TNFis response (LoE 4).

Autoinflammatory diseases comprise two groups, classical monogenetic syndromes and multifactorial or multigenetic inflammatory diseases. The group of monogenic disorders are related to mutations of several genes e.g. involved in inflammasome, interferone or NFkβ pathways. Among those, Familial Mediterranean Fever, (FMF), Early onset Sarcoidosis, TNF Receptor-Associated Periodic Syndrome (TRAPS) and Cryopyrin-Associated Periodic Syndrome (CAPS) are caused by mutations of the following genes: Mediterranean Fever (MEFV), NOD: nucleotide-binding oligomerization domain (NOD); TNF-receptor superfamily 1° (TNFRSF1A) and nucleotide-binding domain, leucine-rich repeat, and pyrin domain containing protein-3 (NLRP3), respectively [96]. SpA as multifactorial disease shows features typical for an autoinflammatory disease, including recurrent inflammatory episodes. Further, it is known that innate and adaptive immunity are strictly interconnected [97]. Data available on MEFV CARD 15 NOD 2 TNFRSF 1 A and NLRP 3 gene mutations for predicting therapeutic response in SpA are absent and therefore not useful for personalization of therapy in the clinical setting. We identified just one study conducted on 137 SpA (82 with PsA and 55 with AS) patients, in which AS risk showed to depend not only on HLA B 27 but also on the protective TNFA haplotype 1031 C/ 308 G. In this study, the TNFRSF 1 A c 625 10 A>G showed a potential factor impacting on the response to TNFis [98].

4.3 Could the "immunophenotype" (phenotypic differences in peripheral helper T cells by flow cytometry) be considered as a biomarker predicting treatment response among different bDMARDs (TNFis, IL17is, IL12/23is) in PsA patients?

4.3.1 In PsA, preliminary results suggest that a strategic treatment based on peripheral T lymphocytes predominant type might address the choice of bDMARDs (TNFis, IL17Ais, and IL12/23is). Both in PsA and axSpA, no other peripheral flow cytometry patterns can be considered biomarkers of treatment response to any bDMARD (LoE 2b).

PsA provides four main phenotypic subgroups of peripheral helper T lymphocyte, as characterized by flow cytometric analysis: activated Th17-dominant, Th1-dominant, both and neither of them [99]. A few studies have investigated the selection of specific bDMARDs based on characteristic lymphocyte phenotypes for treating PsA [100]. Among those, a recent study conducted on 64 patients with PsA. Subjects were classified into the following four types

based on peripheral blood analysis: (i) CXCR3+CCR6-CD38+HLA-DR+ activated Th1 cell predominant type, (ii) CXCR3-CCR6+ CD38+HLA-DR+ activated Th17 cell predominant type, (iii) Th1/Th17-high type and (iv) Th1/Th17-low type [100]. A standard bDMARD treatment group has been compared with a flow-cytometry based strategic bDMARD group, in which the anti-IL12 agent, ustekinumab, was administered to the activated Th1 cell predominant patients, the anti-IL17 agent, secukinumab, to the activated Th17 cell-predominant patients, secukinumab or TNF inhibitor to the Th1/Th17-high patients, and TNF inhibitor to the Th1/Th17-low patients [100]. After 6 months of treatment, there was a significant decrease in simplified disease activity index (SDAI) (from 16.2 to 3.52), DAS28 (ESR) (from 4.13 to 2.27) and psoriasis area and severity index (from 8.36 to 2.40). Low disease activity by SDAI was achieved in 24 (92.3%) of the 26 patients. The rate of low disease activity achievement according to SDAI at 6 months was significantly higher in the strategic bDMARDs treatment group compared with that of the standard bDMARDs treatment group [100]. Frequencies of Th17 have been found significantly decreased in patients who respond to anti-TNF-α therapy, and significantly increased in non-responders. Frequencies of Th17 were positively correlated with BASDAI and BASFI scores [101].

4.4 Could synovitis/enthesitis hystological patterns address therapies?

4.4.1 In PsA, no synovial tissue immunohistochemical patterns can be considered conclusively linked to treatment response to both csDMARDs and bDMARDs (LoE 4).

Several studies have focused their attention on possible correlation between synovial and entheseal tissues biomarkers analysis and therapies. Changes in CD163 (resident tissue macrophages) in the lining and CD163, MMP3, expression and myeloid-related protein 14 (MRP-14; infiltrating myeloid cells) in the sublining have been found able to identify effective response to therapy in SpA [102]. ΔCD3 has been reported as a synovial biomarker of disease response in PsA patients treated with a biologic agent [103]. Adalimumab therapy in PsA is associated with a marked reduction in T cell infiltration in synovial tissue. This parameter has been suggested as a potential biomarker that is sensitive to change after therapy with TNFis [104]. We found two studies performing proteomic synovium analysis and expression differences in response to anti-TNF- treatment. Among those, a difference in-gel electrophoresis (DIGE) based strategy has demonstrated that anti-TNF therapy caused detectable changes in protein expression levels in PsA synovial tissue and that it may be possible to predict subsequent response to anti-TNF therapy by the measurement of protein expression levels before treatment commencement. Preliminary multiple reaction monitoring

(MRM) measurements have illustrated the suitability of this methodology to validate the list of potential biomarkers (albumin, apolipoprotein AI, serum amyloid P, haptoglobin) generated in the DIGE-based studies in a potentially high through put and multiplexed manner [105]. The second study selected a panel of 107 proteins and developed targeted mass spectrometry MRM assays for 57 of the proteins. Results from this study showed that a multiplexed protein assay of a panel of biomarkers that predict response to treatment could be developed [106]. Some of the predictive proteins include S100-A8, S100-A10, Ig kappa chain C, fibrinogen-α and γ, haptoglobin, annexin A1 and A2, collagen alpha-2, vitronectin, alpha-1 acid glycoprotein, cofilin, prolargin, 14-3-3 protein epsilon and clusterin isoform 1 [106].

5. SLE working group

5.1 Refractory lupus nephritis: are there any biomarkers which can suggest when we should use rituximab and when tacrolimus?

5.1.1 There is no evidence that any biomarkers can support the use of rituximab or tacrolimus in refractory lupus nephritis (LoE 5).

The term refractory lupus nephritis (LN) is frequently used in the context of renal involvement in systemic lupus erythematosus with persisting or worsening renal disease activity despite therapy [107]. Understanding the causes of refractory disease and implementing treatment strategies is crucial because this condition is more likely to develop poor outcomes, especially end-stage renal disease. The latest EULAR recommendations suggest that RTX may be considered in refractory or relapsing disease, despite the randomized controlled LUNAR trial failed to show any additive effect of RTX beyond a steroid–mycophenolate mofetil combination for LN type III/IV/V in incident patients [108]. During the last decade, RTX has been reported to be a promising treatment option in several case series and off-label studies in patients with refractory LN [109, 110]. Recently, calcineurin inhibitors, especially tacrolimus, have shown encouraging results in the treatment of proliferative disease with refractory nephrotic syndrome, either alone or in the form of a multitarget therapy (combination of tacrolimus with mycophenolate mofetil). Most of the evidence has been published in the Asian population, including small observational case series with short follow-up and these preliminary data will have to be proven in studies with longer duration and multi-ethnic populations [111-114]. For the topic of refractory LN treated with RTX or tacrolimus, a total of 641 articles were identified, 12 considered eligible for final

analysis including one randomized controlled trial and 11 observational studies (5 prospective and 6 retrospective studies). No direct comparison studies have been retrieved and therefore, to date, there is no evidence that any biomarkers can support the use of RTX over tacrolimus in refractory LN.

5.1.2 In refractory lupus nephritis treated with rituximab the presence of subnephrotic proteinuria and C1q autoantibodies seems to predict the response, while the presence of glomeruli showing active cellular crescents seems to predict a poor renal outcome (LoE 2b).

Understanding which factors are associated with response to rituximab is relevant to optimise and better target its use in refractory lupus nephritis. Overall, biomarkers associated with response to rituximab were assessed in eight studies. An RCT compared the effects of RTX and cyclophosphamide on the serum levels of anti-C1q antibodies and antineutrophil cytoplasmic (ANCA) autoantibodies. In this study reduced serum levels of anti-C1q and ANCA during treatment were directly related to the improvement in prognosis over time, nevertheless, ANCA were not included in the final recommendation for lack of agreement between the experts due to the very low quality of evidence [115]. The efficacy of RTX, alone or combined with mycophenolate mofetil, was reported in patients with baseline subnephrotic proteinuria (< 3.5 g/die) [116, 117], conversely a high percentage of glomeruli showing active cellular crescents was a key predictor of poor renal outcome in one small cohort study [118]. Finally, some studies assessed baseline levels of biomarkers including anti-dsDNA antibodies and low complement levels, but any of these resulted to be a predictor of treatment outcome [118-121].

6. APS working group

6.1 What is the treatment of choice for pregnant women with refractory and/or high risk obstetric APS?

6.1.1 Hydroxychloroquine and low-dose steroid, alone or combined, may be an option for pregnant APS patients with a previous pregnancy refractory to conventional therapy. Intravenous immunoglobulins and plasma exchange, alone or combined, could be considered in refractory high-risk pregnant APS patients (LoE 2b).

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by vascular thrombosis and pregnancy morbidity in the presence of antiphosholipid antibodies (aPL), mainly lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-β2-glycoprotein I

antibodies (anti-β2GPI). Precision Medicine can discriminate the specific profiles of patients with refractory/high risk obstetric APS and those whose aPL become persistently negative, among others. Considered a hallmark of the APS, pregnancy morbidity is one of the features of the current classification criteria [122]. A heparin/low-dose aspirin (LDA) combination constitutes the conventional treatment protocol for pregnant women affected with APS. As this strategy fails in approximately 20-30% of the cases [123], uncovering other options for women refractory to conventional treatment or at high risk of adverse pregnancy outcome has become an urgent undertaking. Some experts in the field are convinced that associating additional treatments before or during pregnancy to conventional therapy will improve these women's live birth rate and/or reduce pregnancy complications that frequently present despite conventional treatment [124]. It is important to remember that all women affected with APS do not face the same risk of poor pregnancy outcome. Although it is indeed true that the treatment of a pregnant APS patient should depend on the level of her obstetric risk, it is not yet clear how maternal-fetal risk of pregnancy complications should be calculated. Several studies have shown that some specific aPL profiles in APS patients are linked to a high risk of poor pregnancy outcome or to being refractory to conventional therapy [125-129]. These profiles include multiple aPL positivity [125] and, in particular, contemporaneous positivity to all three aPL assays (119; 120), lupus anticoagulant activity [128], and high aPL titres [129]. Moreover, some well-defined clinical features such as a history of thromboembolism [124, 130] and/or previous severe pregnancy complications including eclampsia, severe pre-eclampsia, haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and intrauterine growth restriction [126, 131] and/or the presence of a systemic autoimmune disease [126, 128] have been found to be associated to poor pregnancy outcome in pregnant APS women receiving conventional therapy. The ideal management of patients refractory to conventional treatment and/or at high risk of adverse pregnancy outcome remains a challenging question. The SLR outlined here evaluates the effectiveness and safety of the most frequently used additional treatments currently available in an effort to provide clinicians with up-to-date information upon which they can base their treatment decisions.

Nine observational studies (five retrospective and four prospective cohort studies) assessing 505 refractory and/or high-risk APS pregnancies were reviewed. Patients who experienced one or more adverse pregnancy outcome/s while receiving heparin/LDA treatment were considered "refractory," while pregnant APS women with one or more laboratory and one or more clinical risk factors were considered "high risk". The additional treatments that were

evaluated by the review were: hydroxychloroquine (HCQ), low-dose steroids (LDS), plasma exchange (PE), intravenous immunoglobulins (IVIG), inhibitors of tumour necrosis alpha factor (TNFα inhibitors), pravastatin and their combinations. The study's primary outcome was the live birth rate; its secondary outcome was drug-related side effects. A retrospective European multicentre study reported that 14 patients with previous refractory obstetric APS who were prescribed a daily dose of 200-400 mg of HCQ as an additional treatment gave birth to 11 (78%) live singleton births. No drug-related adverse events were registered in the mothers/new-borns [132]. Another retrospective international multicentre study [133] reported a live birth rate of 87.2% in 82/94 women affected with high risk and/or refractory APS pregnancies. The 400 mg dose of HCQ vs the 200 mg one and its administration before but not during pregnancy were the two features that were associated to a significant increase in live birth rate. The study uncovered another unexpected finding: the therapy appeared to be particularly beneficial in the patients who had never experienced a thrombosis but not in those with previous thrombosis ($p = 0.025$). As far as side effects were concerned, one patient discontinued the HCQ therapy at the 12th week of gestation due to diffuse dermatitis. Future investigations will be able to assess the efficacy of different dosages and the long-term safety of HCQ therapy in mothers and infants. For the time being, these data suggest that HCQ can be considered an effective oral treatment when it is used in association with conventional therapy in APS patients with a previous pregnancy loss refractory to conventional therapy. High doses of prednisolone (40-60 mg/day) administered together with LDA are no longer being used because they have been associated with high rates of pregnancy complications [134]. A prospective cohort study examining 23 pregnancies of 18 refractory obstetric APS women reported that low-dose prednisolone (10 mg/day) in addition to heparin/LDA from the time a pregnancy test resulted positive until the 14th week of gestation produced encouraging results. In fact, the live birth rate of those women, which was 4% before they were prescribed this treatment, rose to 61%, and no drug-related side effects were registered [135]. On a negative note, the high-risk patients presenting triple aPL positivity who had experienced previous thromboembolism did not benefit from this additional treatment. Another retrospective multicenter study examining 36 high risk and/or refractory APS women who were prescribed low-dose steroids (10-20 mg prednisone daily) as additional therapy reported a life birth rate of 75% and, again, no side effects were registered [133]. In the same study 19 high risk and/or refractory APS women were treated with low-dose steroid in combination with HCQ in addition to conventional therapy, so obtaining a live birth rate of

63.1% [133]. Although these findings are less sizable with respect to those linked to HCQ treatment, they indicate that low-dose steroids, both alone and combined with HCQ, seems to be effective to prevent poor pregnancy outcome in refractory APS women. Plasma exchange (PE), an extracorporeal blood purification technique that lowers antibody levels, is a treatment option that is prescribed to pregnant women to manage some diseases during pregnancy [136]. In two observational studies 8 and 3 high risk ± refractory APS patients were treated during pregnancy with PE as additional therapy so achieving a live birth rate of 87.5 and 100%, respectively [133, 137]. Adverse events linked to the technique were never registered. To note that all these women were affected by previous thrombosis. Two retrospective studies evaluating the use of IVIG as an additional therapy in 16 and 5 high risk ± refractory APS pregnant patients reported that they respectively achieved a 93.7% and 60% live birth rate [133, 138]. No side effects were observed. An IVIG-PE combination was administered as an additional treatment to 21 high risk ± refractory APS patients, all with triple aPL positivity and 75% with thrombosis, who achieved a live birth rate of 95.2% [133]. Once again, no procedure-related side effects were registered. Similar results had been previously reported by the same authors who conducted a retrospective and a prospective study [139, 140]. In the light of these data, IVIG and PE alone or combined seem to be a reasonable option as an additional therapy for high risk pregnant APS women and, in particular, for in those with triple aPL positivity, a history of thrombosis, and refractory to previous conventional treatment. Finally, due to the exiguous number of homogeneous data regarding the effect of TNFα inhibitors and pravastatin treatments in APS pregnant patients refractory to conventional therapy, for the moment we are unable to comment on the results of those studies [141, 142]. The conclusion that can be drawn from this literature review is that some additional treatments seem to be effective and safe in refractory and/or high-risk APS pregnant patients. The results obtained until now will hopefully indicate the direction of future clinical trials investigating the effect of the different additional treatments in this group of patients and lead to the first steps toward a personalized therapy.

6.2 Can anticoagulation be withdrawn in APS patients whose antiphospholipid antibodies become persistently negative?

6.2.2 In patients with thrombotic APS, who became persistently seronegative (at least for 2 years), with absence or good control of cardiovascular risk factors and with a low risk thrombotic profile, a discontinuation of anticoagulation could be considered (LoE 4).

Long-term oral anticoagulation (OAC) is the standard treatment for thrombotic manifestations in patients with APS. Recent studies suggest that multiple positivity of aPL is more frequently associated with thromboembolic events than a single positive test. Indeed, the so-called triple positive subset of patients (LA + aCL + anti-β2GPI) have been postulated as a group at higher risk to develop clinical features related to thrombosis. Moreover, the risk of thrombosis also increases with the number of positive aPL tests [143]. EULAR recommendations define the aPL profile (high or low risk) by the presence of multiple (double or triple) versus single aPL type, the titre (moderate-high titre vs low titre) and the persistence of aPL positivity in repeated measurements [144]. The definition of the aPL profile is important, in order to determine the intensity of treatment. An accurate assessment of the risk of developing APS manifestation in all individuals with aPL is mandatory for physicians. Thus, in a selected group of patients with a low risk profile (serological and clinical), a short-term anticoagulation therapy could be considered. In "real life", APS patients may have single, double, or triple aPL positivity, with single or multiple isotypes of aCL and anti-β2GPI, and with low versus high titers of antibodies. Special attention has been devoted to a small subset of patients who fulfill APS criteria, but in whom aPL become persistently negative. Therefore, a controversial issue is the possibility to withdraw long-term OAC in these patients, decreasing the risk of bleeding without an excess risk of thrombotic recurrence. For that reason, a systematic review was performed. We included articles that reported the clinical experience of thrombotic APS patients in whom aPL became persistently negative and OAC treatment was withdrawn. Six studies (including 51 patients) that fulfilled the inclusion criteria were analyzed. The first study, performed by Criado-García et al. [145], described six patients with primary APS who became persistently negative for aPL and did not present new thrombosis events during a median of 48 months of follow-up after OAC withdrawal. The second study, published by our group [146], described a series of 11 APS patients, who also became persistently aPL negative, and in whom OAC treatment was withdrawal and no thrombotic events were observed after a median of 20 months. The aPL most frequently detected was LA in 9 (82%) patients. Of note, only one patient presented with arterial thrombosis in both studies. Commarmond et al. [147] published the results of 44 patients in whom OAC was withdrawn, among whom 26 (59.1%) had a primary APS. The main clinical manifestations were thromboembolic (n=63, 40 venous and 23 arterial) and obstetric (n=19) events. Median follow-up period after OAC cessation was 19 months (4–66.75 months). Eleven patients (5 with primary APS, 45.5%) had a recurrent thrombotic

event after OAC withdrawal. Only in one (9%) patient OAC was stopped due prolonged negative aPL and poor treatment adherence, a 21-years old female with APS associated to SLE. After 26 months without treatment, she developed a new pulmonary embolism. The fourth study, led by Riancho-Zarrabeitia et al. [148], focused in 105 pregnant women with positive aPL, 49 of them had primary APS. Treatment was stopped in 13 women and no thrombotic events were observed after a median of 41 (9-135) months. Hindilerden et al. [149] described 3 patients with primary APS, one of them with high risk aPL profile (arterial thrombosis in the presence of triple positivity). No new thrombosis was reported after a median follow-up of 75 months (range 35-119) since OAC was discontinued. Finally, Yelnik et al. [150] reported a retrospective match-control study with 30 APS patients in whom OAC was withdrawn after a median time of 6 months (range, 2-250). Eight of these 30 patients presented aPL disappearance. At the end of study, 13 thrombotic relapses occurred in the 30 APS patients with OAC withdrawal, one of these patients with aPL disappearance. Data of the other 7 patients is missing. None of these patients were included in our analysis due to the lack of data. Overall, only 20 patients (from 3 studies) [145, 146, 149] were included in the final analysis. These patients had primary APS, received initial treatment with OAC, which was subsequently withdrawn after persistent negativization of their aPL titre. No recurrence of thrombosis was observed in a median of 27,5 months. Taking together the existing evidence, results seem to suggest that it is possible to discontinue OAC treatment in some patients with primary APS in whom aPL became persistently negative. However, there is a possibility that in this subset of patients positive aPL was only a transient epiphenomenon and, therefore, may not play a pathogenic role. Another argument to take into consideration is that high-intensity OAC increase the risk of secondary bleeding. Additionally, vitamin K antagonist OAC is complicated in terms of needs of closely and frequent INR monitoring as well as high patient compliance with diet and lifestyle recommendations. Finally, it is important to take into consideration when deciding to stop OAC the role of cardiovascular risk factors and the association with another autoimmune disease. Ideally, OAC could be withdrawn when the risks of treatment outweigh the risks of recurrent thrombosis.

7. pSS working group

7.1 Could pSS patients characteristics influence the response to RTX treatment?

7.1.1 Large RCTs of RTX in pSS failed to reach their respective primary endpoints (LoE 1b), nevertheless RCTs have shown efficacy in treating fatigue and sicca symptoms with improvement

and/or lack of deterioration in salivary flow (LoE 2b). In lower impact studies RTX improved specific domains of pSS disease, including cryoglobulinemic vasculitis (LoE 3b).

pSS is a chronic autoimmune disease characterized by a lymphocytic infiltrate in exocrine glands, mainly salivary glands, associated with sicca symptoms and a wide range of extra glandular manifestations [151]. B cells have a central role in pSS pathogenesis and hyper-activation of these cells, as shown by hypergammaglobulinemia and rheumatoid factor (RF) positivity, identifies a more severe subset of patients at higher risk of systemic involvement and lymphoma development [152, 153]. Therefore, the depletion of B cells with rituximab (RTX), a humanized anti-CD20 monoclonal antibody, has been proposed as therapy for pSS [154]. However, the efficacy of RTX in pSS is controversial and, in the era of precision medicine, the challenge is to still identify predictors of response to RTX, especially in early phases of the disease. On these bases, we conducted a SLR aimed at evaluating clinical and biologic markers of RTX response in pSS; 11 manuscripts were retrieved.

The SLR retrieved 2 large RCTs, and although not reaching their primary endpoints, these suggested the RTX role to treat specific features of the disease. In fact, TRACTISS study, enrolling 110 participants randomised to receive 2 courses of RTX or placebo, pointed out the protective role of such drug on the salivary gland function [155]. In RTX-treated participants, the unstimulated salivary flow (UWSF) was preserved when compared with placebo-treated participants, who showed a reduction of UWSF, after 48 weeks [155]. Further studies with different dosages of RTX, including TEARS study, involving 120 participants randomised to receive 2 RTX infusions or placebo, also showed the improvement of fatigue in these patients, even if the outcome was measured by different indexes [155-162]. In addition, RTX was used to treat severe systemic pSS manifestations, including vasculitic neuropathy, purpura, cryoglobulinemia and pulmonary involvement as reported. In 30 randomised participants treated with RTX or placebo, Meijer et al. showed the RTX efficacy in reducing the number of extra-glandular manifestations, after 12 weeks [161]. In the RTX-treated group, participants showed an improvement in vasculitis, myalgia, and polyneuropathy [161]. Finally, Gottenberg et al. prospectively followed 86 pSS patients treated with RTX for 5 years to describe the role of RTX in treating extra-glandular features [163]. The authors reported RTX efficacy and tolerability in these manifestations. The main features that benefited from RTX were articular, vasculitis, hematologic, pulmonary, and renal ones [163].

7.1.2 RTX treatment is associated with a reduction in B-cell hyperactivity in the blood, but this cannot predict the clinical response (LoE 2b). The serum level of BAFF at baseline is associated

to the rate of B cell repopulation but is not associated with clinical response to RTX treatment (LoE 2b). The number of B cells in the salivary glands at baseline could predict the response to RTX in pSS patients (LoE 3b). The change in B cell number from baseline in parotid gland biopsy but not in minor salivary gland biopsy after RTX is associated with response to RTX (LoE 3b).

Biomarkers of B cell activation, such as gamma globulin levels and RF in serum, are reduced after RTX treatment, but their levels at baseline were not able to distinguish RTX responders from non-responders, as shown in different studies [156, 159, 161, 164, 165]. Notably, B cell activating factor (BAFF) serum levels were found to be positively associated to serum B-cell activity markers and the B cell proportion in salivary glands (SGs) in a post-hoc analysis of TEARS study [166]. BAFF, anti-SSA60 and anti-SSA52 antibodies baseline serum levels were found to be significantly higher in RTX non-responder participants compared to RTX responders, after 24 weeks [166]. Furthermore, in the same study, high grade infiltrate in the minor SGs was associated with a lack of clinical response according to Sjögren's Syndrome Responder Index (SSRI)-30, to RTX treatment [166]. On the contrary, in another cohort of 30 pSS patients, Delli et al. found that the absolute number of B cells in the parotid glands was positively associated with the response to RTX treatment [167]. These data could highlight the importance of patients 'selection and the difference between major and minor SGs involvement in pSS.

7.1.3 Patient stratification based on patient reported outcomes (ESSPRI, HADS) can help predicting patients with a better response to RTX for stimulated salivary flow (LoE 2b).

Patient's symptom-based stratification has shown to identify patients who will more benefit to RTX treatment. Tarn et al. identified 5 different subsets of patients based on hierarchical cluster analysis of five common pSS symptoms: pain, fatigue, dryness, anxiety, and depression. In this manner, the authors identified 4 key clusters of pSS patients, the low symptom burden (LSB), the high symptom burden (HSB), the dryness dominant with fatigue (DDF), and the pain dominant with fatigue (PDF) [168]. Using these clusters, the authors stratified the patients enrolled in the TRACTISS study, in order to understand if different clusters could have a different response to RTX. To date, the patients in the DDF group receiving RTX had significantly higher UWSF and stimulated salivary flow than those receiving placebo, after 48 weeks [168]. This study suggested a symptom-based stratification of pSS patients which could be a meaningful approach in assessing clinical heterogeneity of pSS and possibly reflecting differences in RTX response.

After the SLR was performed the EULAR recommendations for pSS management were published synthesizing all the current knowledge on this topic [169]. These guidelines are based on 9 RCTs, 18 prospective studies and 5 case-control studies and provide a useful guide for pSS treatment. At the same time, the Authors pointed out also the lacking of disease-modifying drugs highlighting the needs of more robust data and encouraging paper like this one, aimed to review the available literature to identify all the unmet needs in pSS management.

8. SSc working group

8.1. What are the patient characteristics (clinical and/or biological and or imaging) that could confer an advantage in terms of survival (or good response) after HSCT?

8.1 Smoking negatively affects survival of patients with SSc that undergo AHSCT (LoE 2a)

Despite current therapies, diffuse cutaneous Systemic Sclerosis (dcSSc) often has a devastating outcome. At present, Autologous Haematopoietic Stem Cell Transplantation (AHSCT) has been proposed as a therapeutic modality for high-risk patients, i.e rapidly progressive dcSSc, early stages of the disease and/or diffuse skin involvement, but in the absence of pulmonary arterial hypertension and/or cardiac involvement. However, AHSCT is associated with an increased early treatment-related mortality. In the post-hoc subgroup analysis of an open-label, multicenter, randomized, controlled phase III trial (Autologous Stem Cell Transplantation International Scleroderma, [ASTIS]), including 79 patients that underwent AHSCT, seven of eight patients, who died for treatment-related causes in the transplantation arm, were smokers [170]. Similar findings were reported in another open label, multicenter, randomized, controlled phase III trial (Scleroderma: Cyclophosphamide or Transplantation [SCOT]), that included 36 patients that underwent AHSCT. In SCOT trial, post hoc analysis, the overall benefit of transplantation was not maintained in smokers [171]. Therefore, the exclusion of patients with a current or former smoking status from AHSCT should be considered.

9.0 Discussion

AIDs are a group of very heterogeneous diseases and it is not surprisingly the wide range of response to therapies along the history of the disease [3]. During the past years, treatment strategies for AIDs have shifted to very specific drugs, which target signalling pathways responsible for autoimmunity and disease progress [172]. On these bases, recognizing the

predictive factors to establish the right drug, for the right patient during the right time, is more essential than ever.

As in the last years PM has been claimed as a revolutionary step for more effective and safe treatment selection [173-174], thus we aimed to understand the PM role and viability in AIDs. The purpose of this work was to obtain a complete overview about PM principles in AIDs. Following the present SLR, an international board of Experts provided different statements, which summarize the current knowledge about the role of PM in AIDs treatment (Table 1), to make physicians more conscious about the predictive factors of good response. Furthermore, our work synthesises key points and new information, from recent or ongoing medical researches derived from technical review, which could have implications for improving the management of these patients.

In order to have a more effective treatment with minimal adverse effects, it is critical to revise contemporary therapeutic strategies. In fact, current drugs for AIDs have the potency to be used in more effective ways and PM could provide enough data to establish the right drug for the right patients [173, 175-177]. The first step is to recognize genetic and molecular profile of those who have been diagnosed with AIDs [178]. As the next step, analysing those profiles as well as considering the previous reports [3] could help us to find the optimum drug and the "window of opportunity" to possibly change the course of a disease improving the long-term outcome of these diseases [175-181].

This work has some limitations related to the use method and to the subjects of our SLR, and all the results should be cautiously interpreted. The main limitation is related to the poor quality of the majority of the included studies, mainly observational studies providing less reliable findings when compared with possible randomised controlled trials specifically designed. On these bases, it could be difficult to perform comparisons between extracted data, thus future specifically designed studies are needed to better clarify these issues.

In conclusion, the results derived from our SLR and International Experts' Consensus confirmed that PM could help in the better usage of available drugs in AIDs management, but further studies are needed. PM would be the future of AIDs treatments, upgrading our ability in the management of these patients, improving treatment strategies efficacy and safety.

Table 1. Statements elaborated following SLR and Experts Consensus

Statements	LoE	Agreement
RA working group		
There is no association between inflammatory markers at baseline (CRP, ESR) and attainment of response when using composite measures that include CRP and/or ESR e.g. DAS28 remission or EULAR response, following tocilizumab treatment in RA.	2b	89%
Higher levels of CRP are associated with lower tocilizumab discontinuation in RA.	4	81%
In RA, obesity does not appear to influence response rates (good EULAR response and drug retention rate) to both abatacept§ and tocilizumab¥. On the contrary, obesity seems to impair the response with TNFisΦ. Conflicting data are available on rituximab¥.	§2b Φ3b ¥4	86%
Anakinra appears to have a bidirectional efficacy, on both glycaemic and inflammatory parameters, in patients with RA and comorbid T2D.	2b	79%
In RA, rituximab induces a depletion of circulating B cells in all treated patients, thus the level of B cell depletion in the peripheral blood after the first infusion does not predict response.	2b	78%
Spondyloarthritides working group		
No work addressed the potential role of HLACw6 and ERAP1 in prediction of treatment response to csDMARDs and bDMARDs in SpA patients. More data were available on HLAB27 status in predicting therapeutic response in SpA and these were moderately useful for personalization of therapy in the clinical setting.	2b	86%
Both in PsA and axSpA, there are no data on HLA-Cw6, ERAP1, MEFV, CARD15/NOD2, TNFRSF1A, and NLRP3 as potential biomarkers for treatment response to bDMARDs (TNFis, IL17Ais, and IL12/23is) or csDMARDs. In axSpA, HLA-B27 could be considered a biomarker of TNFis response.	4	86%
In PsA, preliminary results suggest that a strategic treatment based on peripheral T lymphocytes predominant type might address the choice of bDMARDs (TNFis, IL17Ais, and IL12/23is). Both in PsA and axSpA, no other peripheral flow cytometry patterns can be considered biomarkers of treatment response to any bDMARD.	2b	83%
In PsA, no synovial tissue immunohistochemical patterns can be considered conclusively linked to treatment response to both csDMARDs and bDMARDs.	4	83%

SLE working group		
There is no evidence that any biomarkers can support the use of rituximab or tacrolimus in refractory lupus nephritis.	5	87%
In refractory lupus nephritis treated with rituximab the presence of subnephrotic proteinuria and C1q autoantibodies seems to predict the response; while the presence of glomeruli showing active cellular crescents seems to predict a poor renal outcome.	2b	69%
APS working group		
Hydroxychloroquine and low-dose steroid, alone or combined, may be an option for pregnant APS patients with a previous pregnancy refractory to conventional therapy. Intravenous immunoglobulins and plasma exchange, alone or combined, could be considered in refractory high-risk pregnant APS patients.	2b	100%
In patients with thrombotic APS, who became persistently seronegative (at least for 2 years), with absence or good control of cardiovascular risk factors and with a low risk thrombotic profile, a discontinuation of anticoagulation could be considered.	4	74%
pSS working group		
Large RCTs of RTX in pSS failed to reach their respective primary endpoints§, nevertheless RCTs have shown efficacy in treating fatigue and sicca symptoms with improvement and/or lack of deterioration in salivary flowΦ. In lower impact studies RTX improved specific domains of pSS disease, including cryoglobulinemic vasculitis¥.	§1b Φ2b ¥3b	93%
RTX treatment is associated with a reduction in B-cell hyperactivity in the blood, but this cannot predict the clinical responseΦ. The serum level of BAFF at baseline is associated to the rate of B cell repopulation but is not associated with clinical response to RTX treatment Φ. The number of B cells in the salivary glands at baseline could predict the response to RTX in pSS patients¥. The change in B cell number from baseline in parotid gland biopsy but not in minor salivary gland biopsy after RTX is associated with response to RTX¥.	Φ2b ¥3b	92%
Patient stratification based on patient reported outcomes (ESSPRI, HADS) can help predicting patients with a better response to RTX for stimulated salivary flow.	2b	88%

SSc working group		
Smoking negatively affects survival of patients with SSc that undergo AHSCT.	2a	92%

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Competing interest

None declared for this work.

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