Review

International consensus: What else can we do to improve diagnosis and therapeutic strategies in patients affected by autoimmune rheumatic diseases (rheumatoid arthritis, spondyloarthritides, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome and Sjogren's syndrome)?

The unmet needs and the clinical grey zone in autoimmune disease management

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A B S T R A C T

Autoimmune diseases are a complex set of diseases characterized by immune system activation and, although many progresses have been done in the last 15 years, several unmet needs in the management of these patients may be still identified.

Recently, a panel of international Experts, divided in different working groups according to their clinical and sci-entific expertise, were asked to identify, debate and formulate a list of key unmet needs within the field of rheu-matology, serving as a roadmap for research as well as support for clinicians. After a systematic review of the literature, the results and the discussions from each working group were summarised in different statements. Due to the differences among the diseases and their heterogeneity, a large number of statements was produced and voted by the Experts to reach a consensus in a plenary session. At all the steps of this process, including the initial discussions by the steering committee, the identification of the unmet needs, the expansion of the working group and finally the development of statements, a large agreement was attained.

This work confirmed that several unmet needs may be identified and despite the development of new therapeutic strategies as well as a better understanding of the effects of existing therapies, many open questions still remain in this field, suggesting a research agenda for the future and specific clinical suggestions which may allow physicians to better manage those clinical conditions still lacking of scientific clarity.

1. Introduction

Autoimmune rheumatologic diseases, pathogenic conditions arising from an abnormal immune response, have been increasingly recognized over the past hundreds of years. The possible causes are not fully understood and both cellular and molecular mechanisms are involved [1,2]. Recently, insights into genetic susceptibility show that environmental triggers may be involved, acting via cellular pathways containing disease-associated polymorphisms. The target tissue provides a decisive microenvironment that affects immune-cell differentiation, leading to a chronic activation of immune system and, thus, development of the autoimmune disease [3,4].

Thus, despite of recent advances both in diagnosis and treatment of rheumatic diseases, clinical remission in our patients cannot be reached in at least 50% of the treated patients and definite criteria to tailor the optimal therapy for any patients are still far away to be identified.

On these bases, an experts meeting was organized in Italy aimed to identify some relevant topics, still waiting for definitive conclusions in 6 different clinical conditions, and successively, after a systematic re-view of the literature, pointed out the level of knowledge for each pre-viously identified unmet needs. The results and the conclusions of this work may allow physicians to better manage those challenges repre-sented by the clinical conditions still lacking of scientific clarity.

2. Methods

The methodology consisted of a different steps process. In a first step, the organizers invited leading National and International Experts, defined on the basis of their citation frequency in the field and previous contributions to similar activities. This committee discussed the unmet needs in the management and in the potential treatment targets of autoimmune rheumatic diseases. In the course of this discussion there was unanimous agreement that defining therapeutic targets and an appropriate strategic treatment approach in autoimmune diseases would be valuable, but that evidence for its validity are still lacking. Thus, it was decided to perform a systematic review of literature (SLR), from 1th Jan-uary 2000 until 31th July 2015, and search terms were formulated fol-lowing the Appraisal of Guidelines for Research and Evaluation recommendations [8]. The strength of the selected evidence provided by an individual study depends on the ability of the study design to minimise the possibility of bias and to maximise attribution. 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/). At a subsequent meeting in October 2015 an expanded task force with increased international participation discussed the results of SLR. 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. The discussions took place in separate break-out sessions, devoted to the different topics, and provisional sets of statements were developed. Each group was assigned a “leader” and “rapporteur” in charge of facilitating the discussion and communicating their findings to the conference on the last day in session. During this session, results from each group were summarised, presented, and further input was obtained from the congress. In fact, during the plenary session, certain items were reformulated and reordered and each statement, which was formulated as a draft for voting, in the course of the breakout sessions and by the whole task force, was subjected to voting as ‘yes’ (agreement with the wording) or ‘no’ (disagreement). Statements supported by ≥66% of votes were accepted while the others were rejected outright. After the face-to-face meeting, the statements were distributed to the committee members by email for final com-ments. Only suggestions for improvements of clarity of wording or ad-dressing redundancies were considered, while any change to the meaning was not accepted.

New treatments have been introduced to target different inflammatory pathways and autoimmune rheumatologic diseases. The development of drugs for the treatment of these diseases parallels the increased knowledge of the pathogenic mechanisms. Current treatment guidelines suggest that early diagnosis and initial treatment with immunosuppressive drugs are necessary to limit damage and functional loss and to reduce mortality associated with autoimmune rheumatic disease [5–7]. In this context, it has been shown that frequently the disease course of affected patients is unpredictable as well as their responses, to standard treatments, are variable. Furthermore, it must be pointed out that in many conditions no validated biomarkers exist to predict the course of disease nor the response to therapy.

3. Results

3.1. Rheumatoid arthritis working group

The disease course of Rheumatoid Arthritis (RA) is unpredictable, and despite of different biologic treatments, the complete inhibition of radiographic progression occurs in only half of patients, and about half of patients discontinue treatment within 5 years, independent of the therapeutic strategy employed. No biomarkers currently exist to predict the course of disease [9,10]. On these bases, 13 statements were formu-lated and voted.

3.1.1. The use of biologic drugs in RA: efficacy, time to response and drug survival

Based on direct and indirect comparative studies, no significant differences according to ACR response criteria, functional status, and radiographic progression exist among available biological drugs combined with methotrexate (MTX) in both MTX-naïve and MTX- insufficient responder patients. Level of Evidence (LoE) 1a, Grade of Recommendations (GoR) A.

The only available direct comparison between 2 biological drugs in association with MTX for the treatment of RA has been provided by the 2-year AMPLE trial, demonstrating a similar clinical and radiograph-ic response between abatacept and adalimumab [11]. Several meta-analyses of randomised controlled trials (RCTs) conducted with biologic agents in both MTX-naïve and insufficient responder populations simi-larly showed no significant difference among available biotherapies in terms of clinical response functional status, and radiographic progres-sion [12–18].

The kinetics of response of subcutaneous abatacept and adalimumab are comparable. LoE 1b, GoR A.

In the AMPLE trial, subcutaneous abatacept and adalimumab have been head-to-head compared in a MTX insufficient responder RA population. No significant differences were found in the kinetics of clinical response according to ACR20, 50 and 70 criteria between the 2 drugs [11].

No significant differences in time to response among other biological drugs may be assessed. LoE 5, GoR D.

The comparative analysis of clinical response kinetics between two or more biological drugs may be performed only by head-to-head de-signed RCTs. With the only exception of the AMPLE trial [11], no head-to-head RCT comparing biologic agents in association with MTX have been performed yet. Moreover, real-life data from observational studies about this topic are still lacking.

Based on data coming from main international registries, the long-term drug persistence of etanercept seems to be higher when compared with monoclonal antibodies (adalimumab and infliximab). LoE 2b, GoR B.

Drug retention may be considered a reliable indicator of overall treatment effectiveness in observational registries, as determined by both drug efficacy and safety profile. Thus, many studies from European and US biologic drug registries have provided data about long-term drug retention of tumor necrosis factors inhibitors (TNFi) drugs (espe-cially etanercept, infliximab, and adalimumab) in RA. The majority of those real-life data showed a better retention rate of etanercept com-pared with monoclonal antibodies, especially in terms of long-term drug survival [19–25].

No significant differences in long-term drug retention among other biological drugs may be assessed. LoE 5, GoR D.

Data on drug survival of biological agents other than TNFi coming from observational registries are still limited. The retention rates for abatacept and tocilizumab seems to be similar to what reported for etanercept, but to date a direct comparison has not been performed [26–28].

3.1.2. Biologic drugs in MTX intolerant patients: how effective is monotherapy?

Tocilizumab as monotherapy can be used with a similar efficacy to combination therapy for patients intolerant to MTX. LoE 1b, GoR A.

The ACT-RAY study evaluated 2 different tocilizumab treatment strategies on 556 RA patients. Despite previously MTX treatment, they were randomized either to continue MTX with the addition of toci-lizumab or switched to tocilizumab monotherapy. No clinically relevant superiority of the tocilizumab + MTX add-on strategy over the switch to tocilizumab monotherapy strategy was observed in DAS28-erythro-cyte sedimentation rate (ESR) remission rate at week 24 [29].

Tocilizumab monotherapy demonstrated superiority over adalimumab monotherapy in reducing signs and symptoms of RA

in MTX-intolerant patients, or in whom MTX was considered ineffective or inappropriate. No comparative data against tocilizumab are available for others TNF inhibitors. LoE 1b, GoR A.

Gabay et al. compared the efficacy and safety of tocilizumab monotherapy and adalimumab monotherapy, in 452 RA patients. A significantly greater DAS28-ESR reduction was observed in patients treated with tocilizumab monotherapy when compared with adalimumab monotherapy, for whom MTX was deemed inappropriate [30].

3.1.3. The use of biologic drugs in rheumatoid extra-articular manifestations

Although a worsening of interstitial lung disease has been re-ported in RA patients treated with biologic drugs, the role of biolog-ical therapy is still unclear. LoE 5, GoR D.

Although interstitial lung disease (ILD) is relatively rare in RA, some papers reported increased pulmonary toxicity induced by the biologics and especially the TNFi [31,32]. The drug-induced ILD may be carefully evaluated in patients with pre-existing pulmonary disease requiring biologics [31,32].

Golimumab, infliximab, and especially tocilizumab have been proven to significantly improve anemia, whereas no data are avail-able for other biologic drugs. LoE 1b, GoR B.

It has been shown that approximately 20% of RA patients may pres-ent anaemia. The analyses reported that golimumab, infliximab and tocilizumab may be able to improve haemoglobin levels in RA patients with inflammation inducing anaemia Furthermore, tocilizumab may be more effective than TNFi for improving anaemia and normalizing iron metabolism in RA patients by inhibiting hepcidin production [33– 37].

Vasculitis may be effectively treated with rituximab, whereas no data are available for other biologics. Data from the literature do not show consistent evidence of possible therapeutic effects of biologics on other extra-articular manifestations of RA. LoE 4, GoR C.

Rituximab showed efficacy in rheumatoid vasculitis, that typically affects longstanding seropositive RA patients. A complete vasculitis remission may be observed after 6 months, associated with a lowering of dose of steroids. Further courses of rituximab, may be effective in patients experienced a relapse [38].

3.1.4. Dose adjustments and discontinuation of biologic drugs in patients experiencing clinical remission

In RA patients treated with biologic agents, a possible strategy for maintaining clinical remission and/or low disease activity could be the dose tapering or increasing administration intervals. LoE 1b, GoR A.

Although maintenance of low disease activity states is better with biologic agents continuation, there is some evidence for biologic agents dose reduction without loss of efficacy. In the majority of patients with stable low DAS28 and stable treatment, biologic agents can be down-titrated, which results in a possible reduction in costs [12,39,40].

3.1.5. May biomarkers be predictive of better effectiveness of biological drugs for RA?

Data on genetic, serological, and synovial biomarkers are still controversial and not useful to personalize RA treatment. LoE 5, GoR D.

The use of biomarkers in RA may help in identifying disease risk, im-proving diagnosis and prognosis and assessing the response to treatment [41,42].

Some predictors are consistently predictive while several others are promising but await replication. Nevertheless, these biomarkers still require rigorous validation and have yet to make their way into clinical practice and therapeutic development. The challenge now is to design studies to validate all explored and promising findings individually and in combination to make these biomarkers relevant to clinical practice. Before that, no clinically useful baseline biomarkers can be used in individually tailored biologic treatment in RA [43].

The positivity of rheumatoid factor (RF) and/or anti–citrullinated protein antibody (ACPA) could be useful to drive the choice to rituximab. LoE 2, GoR C.

Data coming from International registries and systematic reviews and meta-analyses support the role of RF and ACPA in driving the choice of B-cell depleting therapy with rituximab in RA, as second-line treatment after failure of the first biologic agent. However, ad hoc studies are lacking, thus strategy based on autoantibody profile still needs to be validated in RA [44–47].

3.2. Spondyloarthritides working group

The spondyloarthritides (SpA) include ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), inflammatory bowel dis-ease-associated spondyloarthropathy, and undifferentiated spondyloarthropathy [48,49]. Classification criteria for axSpA have been recently developed [48,49]. By using these criteria, patients may be classified as non-radiographic axial SpA (nr-axSpA), radiographic axial (ax)SpA or AS. Although biologic therapies showed a strong effect on the clinical outcome of these patients still less is known about their impact on radiographic progression and damage. On these bases, 10 statements were formulated and voted.

3.2.1. Does still exist a place forNSAIDs and sulfasalazine in the treatment of SpA?

Continuous NSAIDs treatment might be efficacy on slowing ra-diographic progression in the spine of AS patients. LoE 1a, GoR A.

Non-steroidal anti-inflammatory drugs (NSAIDs), are recommended as first-line drug treatment for AS patients [50–52]. Continuous treatment with NSAIDs is preferred for patients with persistently active, symptomatic disease. Recently, a meta-analysis of randomized control trials showed that continuous NSAIDs treatment, rather than on-de-mand use, may be effective in retarding radiographic progression, espe-cially in certain subgroups of patients, such as patients with high C reactive protein (CRP). Nevertheless, cardiovascular, gastrointestinal and renal risks should be taken into account when prescribing NSAIDs in these patients [53].

Continuous NSAIDs treatment seems to be not efficacy on slowing radiographic progression in the spine of nrAxSpA. LoE 3b, GoR B.

Although NSAIDs treatment may be associated with retarded radiographic spinal progression in AS, this effect is less evident in nrAxalSpA. In this subset, the positive effect on radiographic progression may be lost due to the relatively low progression rate, in this subgroup. Further-more, in this group, is still not clarify if the pathogenic damage may be oriented toward erosion more than new bone formation [54].

Sulfasalazine might be efficacy in slowing sacroiliac radiographic progression in patients with nrAxSpA but not in AS. LoE 2b, GoR B.

Sulfasalazine (SSZ) has been used as a second-line approach for SpA patients refractory or intolerant to NSAIDs. The evidence supporting a role for this drug in AS is still controversial. However, SSZ seems to slow sacroiliac radiographic progression in nrAxSpa in which a reduc-tion of radiographic progression has been pointed out [55,56].

3.2.2. The use of biologic drugs in SpA: clinical efficacy, radiographic progression and predictors of response

TNFi might be efficacy in slowing radiographic progression in pa-tients with AS. Loe 3b, GoR B.

Although patients with prevalent radiographic damage are prone to develop a more severe disease over time, there is some evidence that TNFi treatment might decelerate the radiographic progression [57–61].

TNFi might be efficacy in slowing radiographic progression in pa-tients with nrAxSpA. LoE 3b, GoR B.

In a monocentric study, patients with active nr-axSpA were treated with adalimumab for 24 months. Adalimumab improved the radiological outcomes, via the assessment of the radiograph of the spine and sacroiliac joints and magnetic resonance of the sacroiliac joints, after 2-years of follow-up [62].

TNFi showed efficacy in reducing disease activity in both AS and nrAxSpA, without significant differences between the different molecules. LoE 1a, GoR A.

The introduction of TNFi marked a turning point in the management of SpA. Different meta-analyses showed that the different TNFi may sig-nificantly improve the disease activity for both AS and nr-axSpA pa-tients, when compared with placebo. No difference among the different molecules were pointed out [63–65].

Infliximab biosimilar is equivalent to infliximab in terms of efficacy. No data are available on slowing disease progression. LoE 1b, GoR A.

In September 2013, the first biosimilar therapy (CT-P13) was li-censed in the EU for the treatment of AS, after the results of the PLANETAS study [66]. Recently, a meta-analysis of available RCTs, to compare the efficacy and safety of infliximab-biosimilar with other bio-logical drugs for the treatment of AS, was performed. This meta-analysis showed no significant difference in the efficacy of infliximab-biosimilar and other TNFi in terms of ASAS20 improvement. No data are available on slowing disease progression [67].

ESR, CRP, Ankylosing Spondylitis Disease Activity Score (ASDAS) and male gender are independent baseline predictors of response and/or continuation of TNFi. LoE 2b, GoR B.

In the Groningen Leeuwarden Ankylosing Spondylitis (GLAS) study, an ongoing prospective longitudinal observational cohort study with follow-up visits according to a fixed protocol, AS naive patients starting infliximab, etanercept or adalimumab were included. Male gender, higher inflammatory markers, both ESR and CRP, higher ASDAS score, were identified as independent baseline predictors of response and/or continuation of TNFi. In contrast, higher baseline BASDAI score was independently associated with treatment discontinuation [68].

3.2.3. Clinical remission in SpA: is it possible to modify or discontinue biologic drugs?

Discontinuation of pharmacologic treatments might be tried in AS patients but high frequency of relapse is predictable (50% in 6 months, 70% in 1 year, 100% in 3 years). LoE 2b, GoR B.

In the study of Baraliakos X et al., AS patients received infliximab for 3 years. At the end of the study patients had the opportunity to continue or not the treatment. The discontinuation of long-term therapy with infliximab in patients with AS leads to a clinical relapse of the disease, with deterioration of signs and symptoms. Patients in partial remission or with low disease activity had a longer duration of benefit after discontinuation than patients with higher disease activity [69].

A tailored approach to reduce doses of TNFi seems to produce similar clinical outcomes at 1 year in AS patients. LoE 3b, GoR B.

Different studies have evaluated the effectiveness of standard versus individually tailored reduced dosages of TNFi in AS patients, achieving low-disease activity. Dose reduction, in these studies, was patient-tailored (step-by-step approach) and consisted of lowering the dose and/or extending the intervals between doses. No difference was observed in the disease activity scores, between the group reducing the dosage and the standard dosage group, at 1 year of follow up [70,71].

3.3. Systemic sclerosis working group

Systemic Sclerosis (SSc) is characterized by immunological alterations, vasculopathy and fibrosis. Despite of several progress both in the knowledge of pathogenic steps and in the therapeutic options, when SSc is compared with other rheumatic conditions, it shows the lowest life expectancy rate [72]. The definite statements are not aimed to cover all the possible unmet needs to be addressed in SSc patients but underlying the aspects that unlike pulmonary hypertension are not usually covered in this field. On these bases, 6 statements were formulated and voted.

3.3.1. Is it possible to increase the overall survival of SSc patients?

Hematopoietic stem cell transplantation (HSCT) has been found to prolong survival in one controlled study. Mycophenolate has been reported to prolong survival in a retrospective cohort study. LoE 2, GoR B.

Autologous HSCT resulted in a higher survival rate compared to intravenous pulse cyclophosphamide [73]. Nonetheless, the high HSCT treatment-related mortality (16.5%) during the first year after treatment make this approach restricted to some selected cases. In a retro-spective single-centre cohort study, which included 172 patients with SSc, mycophenolate, given for >1 year, significantly increased the 5-years survival rate as compared to azatioprine, anti-thymocyte globulin, intravenous or oral cyclophosphamide and MTX [74].

3.3.2. Challenges in SSc management, treatments of specific clinical features No drug has been consistently found to prevent or treat myocar-dial fibrosis. LoE 4, GoR C.

Vasodilatory drugs, such as calcium channel blockers (CCBs) and angiotensin converting enzyme inhibitors (ACEinh) improve myocardial perfusion and on myocardial contractility in short term trials. Moreover, CCBs and ACEinh have been reported to be associated with a preserved left ventricular systolic function and diastolic function, respectively [75,76]. No drug or combination of drugs have been found to affect myocardial disease other than myocarditis.

Mycophenolate, rituximab and imatinib have been reported to be effective in SSc-ILD unresponsive to cyclophosphamide in pro-spective uncontrolled studies. LoE 3, GoR C.

Cyclophosphamide is the only immunosuppressive agent that has shown to be effective, for the treatment of SSc-related ILD, in a randomized, controlled trial [77]. Mycophenolate, rituximab and imatinib have been reported to be effective in SSc-ILD, unresponsive to cyclophosphamide in prospective uncontrolled studies [78].

The proposed treatments for gut fibrosis have only a symptomat-ic effect. LoE 4, GoR D.

Two main unmet needs can be identified in this topic: 1) the lack of appropriate outcome measures to validate each considered symptom; 2) the lack of clinical trials with an adequate patients size. Furthermore, although the majority of symptoms are related to a fibrotic involvement of the gastrointestinal tract, there is no evidence for anti-fibrotic effects of the currently available drugs. Therefore the proposed treatments have only a symptomatic effect [79].

MTX and biological drugs have been found to be effective on ar-thritis in uncontrolled studies. LoE 3, GoR D.

Current treatment strategies for SSc-related inflammatory joint disease have not been evaluated in randomized controlled trials and gener-ally derive from RA studies. Nevertheless, MTX and biological drugs have been found to be effective in SSc associated arthritis in uncon-trolled studies [80].

No drug or therapy has been consistently found to affect disfiguring skin disease LoE 5, GoR D.

Conventional therapy of telangiectasia is based on local light treatment based on pulsed dye laser (PDL) and/or intense pulsed light (IPL). PDL was effective in treating telangiectasia in 8 SSc patients [72]. SSc telangiectasia are more resistant than sporadic telangiectasia to PDL and requires repeated treatment [81]. Skin atrophy is the end stage of skin fibrosis and the best treatment is to prevent or treat fibrosis. There are no studies evaluating drug efficacy in skin atrophy. In lo-calized scleroderma, facial atrophy plastic surgery may be a therapeutic option [82].

3.4. Systemic lupus erythematosus working group

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease affecting any organ in the body. Manifestations may range from mild symptoms to life threatening organ involvement. New insights into SLE pathogenesis have provided new tools for biologic targeted therapies, however the therapeutic strategy in SLE still requires a multi-drug approach with wide immunosuppression. In fact, to date, most randomized controlled trials in SLE have failed and recommendations for disease management are mostly provided according to expert opinion be grounded on clinical evidence [83,84]. Currently, no biologic drug, but belimumab, is approved for SLE treatment, however growing evidence from real life support the use of rituximab even at repeated courses in refractory manifestations. Most data concern refractory Lupus nephritis (LN) and arthritis but hope exists for hematological, skin and neuropsychiatric manifestations as well. Targeted therapy is desirable in SLE due to side effects related to long-standing corticosteroid and immunosuppressive treatment and indeed several efforts in clinical research are aimed to this goal. On these bases, 6 statements were formulated and voted.

3.4.1. The use of biologic drugs in the treatment of specific SLE clinical features

Rituximab can be used in refractory lupus nephritis. LoE 2, GoR B.

LN is a predictor of poor prognosis, affecting nearly 50% of SLE patients over their disease course. Current therapies highlighted in European and American recommendations include mycophenolate mofetil and cyclophosphamide as a first line treatment in proliferative classes. Rituximab is endorsed as a second line treatment in refractory LN with the bulk of evidence coming from case series and notably from controlled or observational studies or registries [83–88]. In fact, prospective and retrospective studies, as well as case series and single case reports, showed 300 patients with refractory LN being treated with RTX at different dosing regimens and analysis revealed complete or partial response to RTX in approximately two thirds of patients [6], while RCTs have failed or were not convincing [89,90]. Interestingly, in the first controlled study heading rituximab versus cyclophosphamide, rituximab looked not inferior [91].

Rituximab and abatacept can be used in refractory arthritis. LoE 3, GoR C.

Arthritis in SLE may range from mild inflammation of the joint to a deforming non-erosive arthritis (heralding Jaccoud's syndrome) or a rheumatoid-like arthritis with bone erosions. Treatment may diverge according to disease severity. Among biologics, rituximab and abatacept were the most likely candidates in light of their effectiveness in rheuma-toid arthritis. Arthritis responded well to rituximab and abatacept in 2 randomized clinical trials [92,93] even though the evidence was not supported due to the randomized clinical trial failure. Most data on ri-tuximab and abatacept on arthritis are provided by registries or case series.

TNFi can be used in refractory arthritis only for a short period of time. LoE 3, GoR C.

Anti-TNF drugs are hardly advisable in SLE due to the risk of trigger-ing autoimmunity, even though TNF is highly expressed in lupus target tissue due to local inflammation. TNF inhibitors were reported effective in small case series showing beneficial effects on arthritis, emophagocytic syndrome or skin lesions [94].

Rituximab can be used in refractory hemolytic anemia, thrombocytopenia, mucocutaneous and neuropsychiatric lupus manifestations. LoE 3, GoR C.

Few data are available on rituximab in refractory severe SLE manifestations. Some cases reported a successful experience in neuropsychiatric, hematological and severe mucocutaneous involvement [95]. Particularly, rituximab use was suggested in refractory thrombocytopenia [96] with most data coming from case reports or small case series; however, strong compelling evidence is still lacking.

The attention was focused on women who presented clinical and/or laboratory criteria that are not sufficient to classify them as affected by

To date there are no sufficient datato support the use of other bi-ologics. LoE 5, GoR D.

New biologics are in the pipeline for SLE that are being studied, which are not yet available. Among them, promising results were provided for interferon (IFN) alpha inhibitors and particularly the anti-IFN receptor inhibitor anifrolumab [97]; other cytokine-targeted thera-py include anti-IL-6 which is currently undervaluation [98].

3.4.2. Corticosteroid-sparing therapies in SLE, a possible role of biologic drugs

Biologics can be used as steroid sparing agents: belimumab and rituximab. Belimumab LoE 1b, GoR A; Rituximab: LoE 3, GoR C.

Sparing steroids in among the emerging therapeutic targets and steroid tapering is supposed to be entailed in a stable remission [99]. Currently, the steroid sparing potential of most widespread biologics in SLE including rituximab and belimumab is increasing. In fact, belimumab was shown to decrease disease activity and flare rate, and accordingly the cumulative steroid dosage required to control disease activity [100].

By the off-label side, rituximab was shown to allow a lower daily prednisone dose in several open label studies and importantly, a longi-tudinal study on 50 LN patients showed how the joint use of rituximab and pulse steroids as initial therapy dramatically reduced the need for oral steroids in the follow-up [101].

3.5. Antiphospholipid syndrome working group

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the coexistence of serological and clinical findings. The circulating antiphospholipid antibodies (aPL) are the serological hallmark. In the classification criteria, the presence of aPL is defined as: lupus anticoagulant (LA) and moderate to high titres of anticardiolipin (aCL) IgG and/or IgM antibodies and/or antiβ2glycoprotein I (aβ2GPI) IgG and/or IgM antibodies. The clinical criteria are defined as the presence of thrombotic events (arterial and/ or venous and/or small vessels) and/or obstetric complications. In the classification criteria, pregnancy morbidity includes three or more re-current early abortions, one or more foetal losses and one or more premature births due to (pre-)eclampsia or placental insufficiency [102]. Despite the recent improving in the understanding of pathogenic mech-anisms, the management of APS patients in some difficult cases could be considered an unmet need [103].

To date, the evidence-based recommendations of 2011 for thromboprophylaxis in patients with APS are based ondata deriving from RCTs and observational studies [104] The state of art of the treatment of patients with APS is based on long-term oral anticoagulation therapy for thrombotic manifestations and the combination of low dose aspirin (LDA) and low molecular weight heparin (LMWH) to prevent obstetric manifestations [105]. Conversely, the management of APS peculiar cases, considered areas of uncertainty, remains still unsolved. This is mainly due to the lack of appropriately designed multicentre studies.

Starting from these recommendations, the purpose of the present report was to better clarify the therapeutic choice in peculiar conditions that we can meet in daily practice. On these bases, 6 statements were formulated and voted. On these bases, 6 statements were formulated and voted.

3.5.1. Challenges in the management ofAPS patients, therapeutic choice in peculiar clinical conditions

Women who presented at least two miscarriages and persistent LA positivity alone should be considered for treatment. LoE 4, GoR D.

Women who experienced two miscarriages and have Sydney laboratory criteria should be considered for treatment. LoE 1b GoR B.

Women with low-titre anti-cardiolipin/anti-beta2GPI and clinical Sydney clinical criteria should be considered for treatment. LoE 2b, GoR B.

APS. In the last years, several obstetric manifestations, in addition to those included in the international consensus criteria, have been pro-

posed as *obstetric morbidity associated with APS* (OMAPS). One of the main dilemmas is whether to treat these patients with non-criteria obstetrical manifestations (i.e. one or two early abortions) or with APS non-criteria laboratory diagnostic tests (low positive aCL or a132GPI). Prospective and retrospective cohort studies suggest that they may benefit from standard treatment for obstetric APS with LMWH plus LDA [106–109].

It could be useful to adopt an "add-on" strategy (hydroxychloroquine, corticosteroids, IVIG, apheresis) in refractory or high-risk (previous thrombosis, previous early severe pregnancy complications) cases of obstetric APS. LoE 2a, GoR C.

Another crucial point is how to treat patients who develop a recurrence of thrombosis and/or pregnancy loss despite the treatment with standard therapy. In case of refractory OAPS or in high-risk OAPS patients (previous thrombosis, previous early severe pregnancy complications), data derive from systematic reviews [106–109]. In these cases, it could be useful to adopt an "add-on" strategy with other drugs such as hydroxychloroquine (HCQ), glucocorticoids, intravenous immunoglobulin (IVIG) or apheresis [110–116].

It could be useful to perform a stronger anticoagulation in APS patients who experienced arterial thrombosis recurrences. LoE 4, GoR D.

Considering APS patients who experienced arterial thrombosis recurrences despite optimal anticoagulation, few data deriving from case report/case series suggest that it could be useful to perform a stron-ger anticoagulation, or an association of anticoagulant treatm.

ent plus LDA, or an "add-on" strategy with HCQ [104].

Medium-high titres and/or triple positive aPL carriers should be considered for treatment with LDA or also with HCQ in case of concomitant autoimmune diseases (such as SLE). LoE 3, GoR C.

The aPL are a heterogeneous group of antibodies directed against toward phospholipid-binding plasma proteins or phospholipid-protein complexes [117]. It is possible to detect aPL also in asymptomatic subjects, the so-called *aPL carriers*. Concerning this group, several questions arestill unsolved, such as the risk of developing thrombotic events and the need of a prophylactic treatment. Few data are available concerning the risk of thrombosis in aPL positive healthy subjects without a con-comitant autoimmune disease [118]. Substantial evidence, reviewed in 2013 by Pengo et al. indicates that a 'triple-positive' aPL profile (pres-ence of LA plus high titres of aCL and a132GPI) is strongly associated with thrombosis, in contrast to positivity for a single aPL [119]. More-over, for aPL carriers risk stratification, a second level analysis could be performed in order to identify antibodies directed against the most pathogenic domain of 132GPI, the domain I (DI). Indeed, the anti-DI 132GPI, or a high DI/DIV-V ratio seem to be more predictive for throm-botic events [120]. Moving from these premises, medium-high titres aPL and/or triple positive aPL and/or more specific subsets of autoanti-bodies in aPL carriers should be considered for treatment with LDA or also with HCQ in case of concomitant autoimmune diseases such as SLE.

3.6. Sjogren's syndrome working group

Sjògren's syndrome (SS) is autoimmune disease mainly affecting of the exocrine glands with associated inflammatory lymphocytic infiltrates of the affected glands. The main symptoms include the dryness of the mouth and eyes deriving from involvement of the salivary and lacrimal glands. Different therapeutic strategies have been proposed for SS; systemic therapy includes steroidal and non-steroidal anti- inflammatory agents, disease-modifying agents, and cytotoxic agents to address the extraglandular manifestations [121,122]. On these bases, 10 statements were formulated and voted.

3.6.1. Suitability of new diagnostic criteria in SS

ACR-EULAR new classification criteria have been developed and validated showing a very good performance in terms of sensitivity and specificity, and a high level of agreement with previously proposed criteria, mainly with American-European Consensus Criteria for Sjögren's Syndrome (AECG) criteria. LoE 1b, GoR A.

The 2016 ACR-EULAR classification criteria [123] for primary (SS) are based on the weighted sum of five items: anti-SSA/Ro antibody positivity and focal lymphocytic sialadenitis with a focus score of k1 foci/ 4 mm^2, each scoring 3; an abnormal Ocular Staining Score of k5 (or van Bijsterveld score of k4), a Schirmer's test result of -S5 mm/5 min and an unstimulated salivary flow rate of -S0.1 mL/min, each scoring 1. A total score of k4 for the above items meet the criteria for SS. Sensitivity and specificity in the final validation cohort were 96% (95% CI 92% to 98%) and 95% (95% CI 92% to 97%), respectively. New criteria showed high level of agreement with previously proposed criteria, mainly with the AECG criteria [123].

The new criteria should represent the gold standard for classification of patients to be enrolled in future studies. Additional criteria of selection can be allowed to select particular subsets of patients for specific studies. LoE 5, GoR D.

Besides the requirement of positive classification criteria, patients with SS may be stratified in subgroups, e.g., patients with positive anti-SSA/SSB antibodies or not, with more or less disease activity, dry-ness, fatigue. The issue of better stratification is being intensively inves-tigated in co-operative international studies. Finally, since the specificity of classification criteria is not 100%, the clinical diagnosis of SS is in any case required in clinical practice.

3.6.2. SS disease activity: from prognosis to therapy

The use of EULAR SS Disease Activity Index (ESSDAI in real-life provides a reliable picture of systemic involvement in SS patients. Measurement of baseline systemic activity by ESSDAI is significantly associated with the prognosis. LoE 2b, GoR B.

ESSDAI is a validated, reliable and sensitive to change tool to mea-sure disease activity in SS patients in daily practice and clinical trials, providing a reliable picture of systemic manifestations in SS, as demon-strated in large cohorts of SS patients [124–127].

Baseline higher ESSDAI scores have been significantly associated with a poor prognosis. SS patients who present at diagnosis an ESSDAI score k14 and/or the presence of predictive immunological markers (lymphopenia, anti-La, monoclonal gammopathy, low complement and/or cryoglobulins), that are strongly associated with overall mortality, are at higher risk of death [128].

The ESSDAI, EULAR SS Patient Reported Index (ESSPRI), patient global assessment and the quality of life should be all evaluated, since they are complementary to assess the disease and since the correlation between them is low. LoE 2b, GoR B.

Data from large cohort studies and therapeutic trials reported that the ESSPRI [129], more than ESSDAI, significantly correlated with health status [130–132] and health-related quality of life measures in SS pa-tients [133–134].

Different studies demonstrated that systemic and patient scores are, however, poorly correlated, suggesting that these measures are complementary in the assessment of the disease and should be separately evaluated [135,136].

The histological assessment and the measurement of salivary flow should be included in SS trials. LoE 5, GoR D.

Routine salivary biopsy has a crucial diagnostic and prognostic value in the assessment of SS patients [137,138]. By integrating histopathological data with clinical and molecular findings, different stages of lymphoproliferation with different risk of lymphoma evolution may be identified [139], providing also a potential useful instrument for patient stratification and for the design of SS trials.

The assessment of salivary gland secretory function, mainly through the measure of stimulated or unstimulated salivary flow rate, might be

useful to stratify SS patients on the basis of their residual secretory potential in order to identify cases with residual salivary function, potential responders to new treatments for what concerns dryness. Thus, the measurement of salivary flow should be included in all SS trials [140,141]. This functional study could be usefully accompanied by salivary gland ultrasonography investigation, to document glandular parenchymal damage and its possible deterioration over time in SS.

3.6.3. May clinical, hematological, and/or histological biomarkers improve SS management?

Clinical (persistent parotid swelling, purpura), hematological (low C4, cryoglobulinemia, leukopenia), and histological (germinal center-like structures) features are still insufficient as biomarkers of SS. Autoantibody formation and hypergammaglobulinemia are associated with extra-glandular manifestations. LoE 3b, GoR C.

Traditional and new clinical and laboratory biomarkers are needed to improve the diagnosis of SS, to categorize subsets of pa-tients, and to unmask pathogenic mechanisms which may represent novel therapeutic targets. LoE 5, GoR D.

Research about biomarkers in SS has been mainly oriented, over the years, to the identification of predictors of evolution to malignant lymphoma, the main cause of SS poor survival and increased mortality [142–145]. Many biomarkers (such as cryoglobulinemia, often linked to cryoglobulinemic vasculitic features; persistent salivary glands swelling, usually parotid enlargement; hypocomplementemia; leukopenia; histologic detection of ectopic germinal center-like structures in salivary glands biopsy) are now available to help in daily practice the individuation of those SS patients at higher lymphoma risk, but they are not still exhaustive and require validation [145–155]. However, biomarkers could likely detect also SS patients more prone to worsen in different sicca or extraglandular manifestations, or more prone to respond to rather different treatments. Much research is currently dedicated to this issues.

Starting from a better comprehension of pathogenic mechanisms underlying SS, future efforts are needed to identify and validate new biomarkers, towards a stratification of well-defined patients subgroups for diagnostic, prognostic and therapeutic purposes.

3.6.4. Therapeutic strategies in SS, from conventional therapies to biologic drugs

Disease-modifying anti-rheumatic drugs (DMARDs) are given for systemic involvement; their administration is based on non-controlled studies and expert opinion. HCQand MTX are effective for ar-thritis, cyclophosphamide for severe vasculitis, small doses/short courses corticosteroids for constitutional symptoms, parotid gland enlargement and arthritis. LoE 5, GoR D.

Evidence-based efficacy of conventional immunosuppressive therapy in SS treatment is limited, due to the lack of large controlled randomized studies orto the design of clinical trials [156–161]. However, expert opinion, non-controlled studies and daily clinical practice support their use [162–164].

Biologics may represent an effective treatment for SS in the future; B-cell depletion appears now recommended mainly for systemic manifestations and for persistent parotid swelling; residual glandular function is a prerequisite to enroll patients in trials to study sicca. LoE 4, GoR D.

Larger multicentre, double blind studies, with the study of histology and biomarkers, are needed, applied in phenotypically homogeneous SS populations to be better stratified. LoE 5, GoR D.

Three biologics, i.e., rituximab, belimumab and abatacept, proved their effectiveness in open studies for some extraglandular features of SS, but not for dryness, in general [165–170]. Parotid swelling, which represents a very important predictor of malignant lymphoma, may respond to these treatments, although any prevention of lymphoma evolution remains hypothetical. Cryoglobulinemic vasculitis benefits from rituximab [171,172]. Of note, upregulation of B-Cell Activatig Factor (BAFF) may play an important role for ongoing B-cell lymphoproliferation [173]: it should be thoroughly investigated, and long-term treatment approaches should be also studied [174].

Patient inclusion criteria, disease duration, concomitant treatments, study endpoints, treatment duration and other parameters markedly differed in previous studies with biologics in SS. Many additional biolog-ic drugs are also under investigation. A better stratification of SS repre-sents a key preliminary step to improve future treatment studies.

4. Discussion

Autoimmune diseases are a complex set of diseases characterized by immune system activation and systemic involvement of the body. Al-though many progresses have been done in the last 15 years, and vari-ous practical guidelines for the management of these patients have been developed and updated in order to improve the care of these patients so far, remission may be reached in <50% of patients and a personalized medicine, in this field, is still far away. Thus, the unmet need for autoimmune diseases care is one of the greatest public health problems in the developed countries. Furthermore, the gaps between guideline and real-world practice, and differences according to the region, culture, and medical environments may be the causes of different unmet needs for autoimmune disease care [175].

On these bases, a panel of international Experts were asked to identify, debate and formulate a list of key unmet needs within the field of rheumatology, serving as roadmap for research as well as support for clinicians. Experts were divided, according to their clinical and scientific expertise, in different disease-specific working groups, searching for the highest scientific answer for the identified unmet needs, within the most common autoimmune rheumatic diseases, by using SLR. To note, despite of the remarkable discoveries of the past 15 years [175–182], in-cluding the introduction of biologic treatments, targeting specific path-ogenic molecules [182–187], the Experts identified several perceived unmet needs which still need a clear scientific definition and fulfilment such as the need to diagnose as early as possible autoimmune rheumatic diseases, to identify those patients developing complications as well as to elaborate therapeutic strategies using available drugs. It must be pointed out that treatment recommendations should usually be based on evidence. However, where evidence is missing, expert opinion has to be considered. Of course, the statements presented in this paper, sometimes may be not based on hard evidence, because strategic ther-apeutic trials, in which therapy was consistently adapted to reach a pre-specified treatment target and compared with a non-steered approach, are currently not available for many autoimmune diseases and available literature is still scarce. While the SRL provided any indirect evidence these statements may be only regarded as expert opinion and confirms the need for more research in the field.

At all the steps of this process, including the initial discussions by the steering committee, the identification of the unmet needs, the expan-sion of the working group and finally the development of statements for all the selected autoimmune rheumatic diseases, a large agreement was attained. Due to the differences among the disease and their het-erogeneity a large number of statements was produced. Several of these statements may be considered as supportive or operational but covering the grey zone of the clinical practice in which no strong evi-denced based recommendations exist, thus possibly helping physicians in the decision-making process.

The Expert panel discussed the using of different drugs in the treatment of rheumatic autoimmune diseases and the possible customized management plans that should be important in these heterogeneous diseases. The majority of the drugs used in this context, mainly biologics, are expensive, and this aspect is always a concern, in those coun-tries in which the health systems are progressively reducing the financial support, thus influencing how appropriately choosing, maintaining and discontinuing the therapy for these patients [182]. Furthermore, the management of comorbidities as well as of complications, is