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Title page

Title

Tailoring the treatment of inflammatory rheumatic diseases by a better stratification and characterization of the clinical patient heterogeneity. Findings from a systematic literature review and Experts' consensus.

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Highlights

- Inflammatory rheumatic diseases are disorders due to a deregulated immune response.
- Patients with inflammatory rheumatic diseases have significant clinical heterogeneity.
- By a better patient profiling, clinicians could balance the therapeutic management.
- Dissecting the patient clinical heterogeneity of patients may improve their treatment.
- Further clinical studies on patient disease subsets may increase the clinical remission.

Abstract

Inflammatory rheumatic diseases are different pathologic conditions associated with a deregulated immune response, codified along a spectrum of disorders, with autoinflammatory and autoimmune diseases as two-end phenotypes of this continuum. Despite pathogenic differences, inflammatory rheumatic diseases are commonly managed with a limited number of immunosuppressive drugs, sometimes with partial evidence or transferring physicians' knowledge in different patients. In addition, several randomized clinical trials, enrolling these patients, did not meet the primary pre-established outcomes and these findings could be linked to the underlying molecular diversities along the spectrum of inflammatory rheumatic disorders. In fact, the resulting patient heterogeneity may be driven by differences in underlying molecular pathology also resulting in variable responses to immunosuppressive drugs. Thus, the identification of different clinical subsets may possibly overcome the major obstacles that limit the development more effective therapeutic strategies for these patients with inflammatory rheumatic diseases. This clinical heterogeneity could require a diverse therapeutic management to improve patient outcomes and increase the frequency of clinical remission. Therefore, the importance of better patient stratification and characterization is increasingly pointed out according to the precision medicine principles, also suggesting a new approach for disease treatment. In fact, based on a better proposed patient profiling, clinicians could more appropriately balance the therapeutic management. On these bases, we synthesized and discussed the available literature about the patient profiling in regard to therapy in the context of inflammatory rheumatic diseases, mainly focusing on randomized clinical trials. We provided an overview of the importance of a better stratification and characterization of the clinical heterogeneity of patients with inflammatory rheumatic diseases identifying this point as crucial in improving the management of these patients.

Keywords

Precision medicine; randomized controlled trials; rheumatoid arthritis; spondylarthritis; systemic lupus erythematosus; Sjogren's disease; systemic sclerosis; adult-onset Still's disease.

Main text

1.0 Introduction

Inflammatory rheumatic diseases are different pathologic conditions associated with a deregulated immune response [1,2]. These may be codified along a spectrum of disorders, with autoinflammatory and autoimmune diseases representing the two-end phenotypes of this continuum [3]. Autoimmune diseases are related to the loss of immune tolerance, the recognition of self-antigens, the recruitment of autoreactive T- and B-cells, followed by the production of autoantibodies and an aberrant adaptive immune response [4-6]. Conversely, autoinflammatory diseases appear to not directed by specific antigens, but these disorders are characterized by apparently unprovoked episodes of systemic inflammation without the production of specific autoantibodies [7-9]. However, there are some overlaps in autoimmunity and autoinflammation features in the inflammatory rheumatic diseases; some 'mixed- pattern' disorders may be indeed suggested in this context [3]. Despite these pathogenic differences, inflammatory rheumatic diseases are commonly managed with a limited number of common immunosuppressive drugs, sometimes with partial evidence or transferring physicians' knowledge in different patients [10,11]. In addition, several clinical trials, enrolling these patients, did not meet the primary pre-established outcomes and these findings could be linked to the underlying molecular diversities along the spectrum of inflammatory rheumatic disorders [12,13]. In fact, the resulting patient heterogeneity may presumably be driven by differences in underlying molecular pathology also resulting in variable responses to immunosuppressive drugs. Thus, the identification of different patient subsets may possibly overcome the major obstacles which strongly limited the development of more effective therapeutic strategies for patients with inflammatory rheumatic diseases [14-16]. Different clinical heterogeneities could indeed advocate a diverse therapeutic management to improve patient outcomes and increasing the possibility to reach and maintain the clinical remission. Therefore, the importance of a better patient stratification and characterization is increasingly pointed out according to the precision medicine principles, also suggesting a new approach for disease treatment and prevention that considers individual variability in genes, environmental exposure, and lifestyle [17,18]. In fact, based on a better proposed patient profiling, clinicians could more appropriately balance the therapeutic management, in guiding the administration of a more aggressive treatment and, at the same time, minimising the exposure to iatrogenic side effect in less severe patients.

Taking together these considerations, a patient-based stratification may be a meaningful approach, addressing the clinical heterogeneity, reflecting possible differences in pathogenic mechanisms, and variable therapeutic responses.

On these bases, we aimed to synthesize and discuss the available literature about the clinical stratification and patient characterization in regard to therapy in the context of inflammatory rheumatic diseases.

2.0 Methodology

The overarching aim of the systematic review of literature (SRL) and Experts' discussion was the clinical profiling in regard to therapy following the main idea that an accurate stratification of patients may improve their management and outcomes. We mainly focused on randomized clinical trials (RCTs), where available, considering the clinical relevance of these data in delineating the general therapeutic strategies.

As performed in previous works [19-21], the general methodology relied on a Delphi Technique aimed to produce, starting from the results of a SRL, a set of statements summarizing the consensus among the Experts, assessing six inflammatory rheumatic diseases, namely rheumatoid arthritis (RA), spondylarthritis, systemic lupus erythematosus (SLE), Sjogren's disease (SjD), systemic sclerosis (SSc), and adult-onset Still's disease (AOSD). The latter was introduced as prototype of an autoinflammatory disease in adults.

Firstly, a group of Experts was identified for each topic, composed by Coordinators, Delegates, and bibliographic Fellows. The members of each working group were selected based on their contributions into the specific fields which were evaluated. After that, each group identified and choose some relevant clinical questions on patient stratification in regard to treatment, needing further and updated clarifications according to published scientific evidence and in conjunction with the Experts' opinion. Assessing available data, from January 1, 2013 to January 1, 2023, the SRL was performed, by bibliographic Fellows, in indexed international Journals (Medline via Pubmed, Scopus, and Cochrane database) by selected relevant clinical questions. The search strategy pooled indexed and free-text keywords, interventions, and outcomes of interest as requested for each topic. PICO methodology served as rephrasing strategy across all working groups, along with the pre-defined "Population", "Intervention", "Comparison", "Outcomes", as requested by each topic research question. The main search was prepared using a string of terms, combining the keywords to increase the precision and accuracy of the research. Moreover, the bibliography of relevant articles

was also hand-searched for the identification of additional relevant items. Included studies were English full-text manuscripts conducted in adult patients with selected inflammatory rheumatic diseases. Also, to be included in the review, studies had to report enough data concerning each single selected topic, otherwise they were excluded. The research was mainly focused on RCTs, where available. Narrative reviews, editorials, conference abstracts, case reports, and preclinical studies were excluded. For each working group, full-texts of articles were screened and selected after assessing titles and abstracts by bibliographic Fellows, then independently verified by Coordinators. Bibliographic fellows independently extracted the results and Coordinators verified the process. All uncertainties and/or disagreements were discussed until reaching a final consensus. The levels of evidence (LoE), suggested by Oxford University, identified the hierarchy of study types (<http://www.cebm.net/oxford-centre-evidencebased-medicine-levels-evidence-march-2009/>). During the meeting, the results of literature analysis were summarized, presented, and additional inputs were obtained in expanded working groups including all Delegates. Conflicting results were further discussed, considering the quality of assessed studies, until reaching an agreement into the single working group. Preliminary statements were consequently formulated according to results and quality of selected articles. Disagreements were discussed until reaching a final consensus. After that, for each selected topic, preliminary statements based on available scientific results were presented in accordance with their level of evidence, discussed, eventually reformulated, and voted through a Delphi-method during a Consensus involving the whole panel of international Experts. In the plenary session, the statements were voted as 'yes' (agreement) or 'no' (disagreement) from the entire panel of Experts. Statements supported by $\geq 66\%$ of positive votes were accepted whereas the others were rejected outright. At this final stage, only suggestions for improvements of clarity wording or addressing redundancies were considered, whereas any change to the meaning was not accepted. This project was concluded in Italy on February 17-18, 2023.

3.0 Rheumatoid arthritis

3.1 Seropositivity (ACPA and/or RF) is associated with an earlier and better response to MTX-based conventional treatment strategy in patients with early rheumatoid arthritis (LoE: 2b). Seropositivity is associated with a more evident reduction of structural damage in rheumatoid arthritis patients under an aggressive, MTX-based, treatment strategy (LoE: 2b).

Methotrexate (MTX) is considered the “anchor drug” for the management of RA patients. As such, international guidelines recommend the use of MTX as first line therapy, together with a treat-to-target approach, aimed at the achievement of remission or, at least, a low disease activity state. In the first step of the algorithm-based strategy for the treatment of RA, the indication for the use of MTX comes irrespective for the autoantibody status, while the presence of RF and/or ACPAs represents a driver for the choice of a targeted therapy in case of failure of conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) [22]. While some data indicate a preferable choice for certain biological DMARDs (bDMARDs) according to serostatus, the question whether profiling RA patients through rheumatoid factor (RF) and anti-citrullinated protein autoantibodies (ACPA) status might be useful to predict response also to conventional therapy remains open.

The IMPROVED trial evaluated the efficacy of a MTX plus prednisone combination therapy in induction of remission in patients with early RA. In this multicenter study, 610 patients with early RA or undifferentiated arthritis were started with MTX 25 mg/week plus prednisone 60 mg, aiming at the remission according to the DAS index. After the first 4 months from induction therapy start, patients not in remission were randomized to add-on therapy with MTX plus hydroxychloroquine plus sulfasalazine, or MTX plus adalimumab. In the 5-year extension of study, ACPA positive patients were more prone to achieve early remission (i.e., within 4 months) under MTX (plus prednisone) treatment compared to seronegative ones [23].

Similar results were obtained through a machine learning approach by the analysis of data derived from 4 RCTs. In the work by Duong and Colleagues, the trajectories of ESR-DAS28 change of 755 early RA patients were evaluated through a latent class analysis. Over 24 weeks of MTX, ACPA positivity appeared to be a predictor of good response of treatment [24]. Interestingly, the higher number of isotypes, the higher likelihood of response under MTX therapy in a post-hoc analysis of the IMPROVED trial. It has been postulated that the presence of multiple autoantibodies at baseline may reflect a more active autoimmune milieu which is more susceptible to suppression by MTX in the initial stages [25].

Not only MTX alone or in combination with corticosteroids, but also MTX-combination therapy with other conventional synthetic DMARDs confers a higher probability to obtain better DAS28-responses in ACPA-positive RA patients, as observed in a post-hoc analysis of the CARDERA trial. In this study, 467 early RA patients were randomized to receive MTX alone or in combination with either cyclosporine A or prednisolone, or with

cyclosporine A plus prednisolone. Triple therapy and corticosteroids were associated with better DAS28 responses over a 6-month follow-up, but only in ACPA positive subjects [26]; however, despite better DAS28 results at 6 months, in an another post-hoc analysis of the same study ACPA positive RA patients displayed no differences in terms of DAS28 remission [27].

The primary aim of a disease-modifying drug is the ability to arrest anatomical damage within the joints, and, consequently, to reduce functional disability and mortality risk. The presence of autoantibodies is a well-described risk factor for radiographic progression, but the influence of ACPA and/or RF positivity on the disease-modifying effect of MTX is not well established [28].

In the aforementioned CARDERA trial, all treatment arms were associated with lower radiographic progression in ACPA positive patients, while no differences were observed in their autoantibody-negative counterparts [26]. Also, an MTX plus TNF inhibitor (TNFi) ab-initio seems to reduce joint damage in RF positive patients, as observed in a post-hoc analysis of the FIN-RACo and NEO-RACo RCTs [29]. This suggests a general greater efficacy of an MTX-based strategy in the presence of autoantibodies.

3.2 Seropositivity is associated with increased efficacy of non-TNFi bDMARDs, especially rituximab (LoE: 1a). Seropositivity is also associated with a better response to abatacept (LoE: 2b) and appears to be associated with a better response to tofacitinib (LoE: 2b).

In modern era, the therapeutic armamentarium for the management of RA has significantly increased, especially thank to the development of new biologic or target synthetic molecules. This highly improves the chance to obtain better disease outcomes. According to international guidelines, patients who fail to achieve at least low disease activity with a first (and, in the absence of risk factors for disease progression such as autoantibodies positivity, a second) course of csDMARD, are strongly suggested to be escalated to a b- or tsDMARD; however, a clear indication on whether prefer a molecule over another's according to RF/ACPA status is still lacking [22].

A large metanalysis of 2139 RA patients extrapolated from four RCTs (REFLEX, SERENE, DANCER and IMAGE study) evaluated the efficacy of B-cells depletion therapy, rituximab at 24 weeks, in accordance with the autoantibody status. The Authors have shown that seropositive patients respond better to rituximab compared to seronegative ones. Interestingly, the magnitude of this effect was not equal in all treatment groups, while the largest impact of serotype in response to rituximab was observed in those

who failed at least one TNFi. These results were similar both for DAS28-ESR index as well as ACR responses [30].

Similarly and in accordance with the pathophysiology of RA, also inhibition of co-stimulation appeared to be more effective in autoantibody-positive disease. In the AMPLE trial, 646 refractory patients to conventional therapy and naïve to bDMARDs were randomized to receive either subcutaneous abatacept or adalimumab, with the primary endpoint of non-inferiority. In a post-hoc analysis performed by Fleischmann and Colleagues, patients with poor prognostic factor, including autoantibody positivity, showed better response to abatacept in terms of disease activity and physical function [31]; interestingly, patients with the highest ACPA concentrations had better response with abatacept, while this association was not observed with adalimumab [32].

Few data are available with respect to other non-TNFi. A post-hoc analysis of data pooled from five RCTs (ORAL Solo, ORAL Sync, ORAL Standard, ORAL Scan, and ORAL Step) concluded that double autoantibody-positive patients treated with tofacitinib were more prone to achieve ACR-responses compared to seronegative ones. Also, double positivity or single ACPA positivity was associated to a higher chance to achieve DAS28 remission or low disease activity than double autoantibody-negativity [33].

3.3 Despite stratification based on definite age cut-off (e.g., >65 vs. < 65 years) is mostly unavailable, age analyzed as continuous variable does not affect response to MTX (LoE: 2b).

Similarly to what has been analyzed for RF and ACPA status, it remains to be clarified whether the age of patients may influence the response to DMARDs in order to guide therapeutic choices. Evaluating age as a predictor of response to MTX in patients affected by RA, we identified 4 RCTs.

In a post-hoc analysis [34] of two RCTs, OPTIMA (a randomized, double-blind, double-period, phase 4 trial) and PREMIER (a phase 3 randomized controlled trial), age was not correlated with the clinical response in patients with early RA treated with MTX.

In an analysis of the OPERA trial [35], where MTX was prescribed and increased to 20 mg/week in combination with placebo or adalimumab, the authors examined the factors predicting hand bone loss. The literature, indeed, suggests that erosions and periarticular bone loss are both characterized by reduced bone formation and increased bone resorption. Baseline age was identified as a predictor of hand bone loss at one year.

In a post hoc analysis of the U-Act-Early trial [36], Teitsma et al. examined clinical predictors for inadequate response to MTX plus hydroxychloroquine. The tREACH trial was utilized for sample validation. The authors didn't find an association between age and the risk of inadequate response to therapy ($p=0.10$, OR 1.03, 95% CI 0.99 - 1.05). In a post-hoc analysis of the CARDERA trial [27], early RA treatment-naïve patients were randomized into four treatment arms: MTX; MTX plus cyclosporine; MTX plus prednisone; MTX plus cyclosporine plus prednisone. The study compared patients aged younger than 50 years to those older than 50 years in terms of DAS28 remission at 24 months. The results suggested that patients aged over 50 years with higher tender joint counts experienced a more favorable response to triple therapy. On the other hand, an age of less than 50 years is a predictor of a good response to all three treatment schemes.

3.4 Age of golimumab start (>65 years vs. ≤65 years) does not affect its efficacy, in patients with RA under the same dosage of MTX. (LoE: 2b). Younger age, analyzed as a continuous variable, is associated with a better response to etanercept, but information about MTX dosage is not available (LoE: 2b).

We identified 5 RCTs that evaluates age as a predictor of response to bDMARDs. In a post-hoc analysis of the GO-FURTHER TRIAL [37], the efficacy of intravenous golimumab plus Methotrexate was evaluated using the American College of Rheumatology response criteria over 112 weeks. The clinical efficacy appears to be comparable between patients aged ≥ 65 years and those younger than 65 years. Notably, the mean MTX dosage was similar between the two groups. In a post hoc analysis of the PRESERVE trial [38], patients with RA demonstrating moderate disease activity were analyzed. In the open label period within the initial 36 weeks, where patients were administered etanercept 50 mg once a week in combination with methotrexate, it was observed that a younger age at baseline, assessed as a continuous variable, was a predictor for achieving remission by week 36, considering DAS28, SDAI, and CDAI. When age was considered as a categorical variable and analyzed using a cutoff of 40 years, as well as comparing groups of patients younger than 40 years and those aged 40 to 65 years, the same result was obtained. In the analysis with 65 years as the cutoff point, it was found that younger patients had a higher probability of achieving remission at week 36, as determined by SDAI and CDAI. However, when considering these groups of patients, age was not predictive of reaching remission evaluated with DAS28. In another post hoc analysis of an RCT conducted with Latin

American patients diagnosed with MTX-resistant RA [39], predictors of response to treatment were evaluated in the group randomized to etanercept 50 mg weekly plus MTX. The analysis revealed that younger age was identified as a predictor of response in this population. Considering age, the optimal cutoff predicting remission at week 24 included an age ≤ 49 years (OR 2.93), and an age ≤ 42 years at week 128 (OR 2.21). On the other hand, in the TEAR trial, a Phase 3 RCT involving early RA patients younger than 65, participants were randomized to introduce etanercept or sulfasalazine plus hydroxychloroquine after 6 months of treatment with MTX. Higher age was found to be associated to Predict Low Disease Activity at 1 year [40].

3.5 Several single nucleotide polymorphisms have been associated with response to bDMARDs; however, their use as predictive biomarkers for treatment response is limited, and the effect size is small (LoE: 1a).

We identified 20 research articles that explored the association between genetic variants, particularly single nucleotide polymorphisms (SNPs), and response to bDMARDs [4-60]. Fifteen were meta-analysis studies [41-48, 52-60], 3 were observational studies [49-52], 1 was a randomized controlled trial [44] and one was a systematic literature review [45]. The articles included investigated different polymorphisms and risk alleles for RA. Among them, 5 studies did not find any association between various bDMARDs (mostly TNFs) and the polymorphisms analyzed [41-54]. The other studies found various associations between treatment response and SNPs [46-60]; however, these were mainly individual studies which haven't been replicated and/or validated. Importantly, The IL-6R polymorphisms rs12083537 and rs1800795 have been associated with either TNFis [60] or tocilizumab (TCZ) [59] response. Three studies showed that IL-6R rs12083537 AA genotype was linked to a better response to TCZ [58-60] while the IL-6R rs1800795 -174*G genotype was associated with a good response to TNFi [60] and IL-6 -174 C allele to a poorer response [55].

Despite some findings have suggested genetic polymorphisms as potential predictive markers of treatment response, the overall utility of these remains limited. Meta-analyses and systematic reviews have highlighted the challenges in replicating genetic associations across different populations and treatment cohorts. Furthermore, the effect sizes observed for most genetic variants are modest, underscoring the complexity of genetic influences on treatment response variability.

3.6 Various genes and miRNAs in peripheral blood have been associated with response to bDMARDs; however, these associations are derived from observational studies, indicating a small effect size and limited clinical utility as predictive biomarkers for treatment response (LoE: 2a).

We identified 12 research studies that considered gene signatures and microRNAs (miRNAs) as potential peripheral blood biomarkers predictive of treatment response to bDMARDs [61-72]. In this context, two RCTs conducted on a population with an early stage of the disease highlighted an association between low levels of miR-22 expression [63] and high levels of miR-27a-3p [64] with response to TNFi. Although many other articles correlated various genes and miRNAs in peripheral blood with treatment response to bDMARDs, these results primarily stem from observational studies.

The small effect size, heterogeneity in study designs, inconsistency in the used clinical outcome and the different patient cohorts included all limit our ability to draw a unique conclusion and their adoption as predictive biomarkers in the clinical practice. Moreover, the clinical utility of peripheral blood biomarkers as standalone predictors of treatment response remains uncertain. Future research efforts should focus on elucidating the biological mechanisms underlying peripheral blood biomarker associations and validating their predictive value in well-designed prospective studies.

3.7 Several serum proteins (OPN, SAA, CXCL13, VICM) have been linked to response to bDMARDs; however, their predictive value for treatment response is limited, and the effect size is small (LoE: 2b/3). In post-hoc analysis of two RCTs, the CXCL13 to sICAM-1 ratio has been implicated in informing response to TNFi versus IL6-receptor inhibition, albeit with contradictory results (LoE: 2a).

Several serum proteins, including Osteopontin (OPN), Serum Amyloid A (SAA), C-X-C Motif Chemokine Ligand 13 (CXCL13), and Vascular Induced Cartilage Metalloproteinase (VICM), have been investigated as potential predictors of treatment response to bDMARDs in RA [73-99]. We included in the analysis 27 research studies (16 clinical RCTs [73, 79-83, 85-89, 95-99] and 11 observational studies [74-78, 84, 90-94]) that examined the role of many serum proteins as biomarkers of treatment response. Most of them [73-86] did not show any significant differences between responders and non-responders to bDMARDs, confirming the challenge of identifying a single biomarker able to predict response. Other non-replicated studies pointed out the association of IL17A [87], SAA [88], CTX-I/OC, CTX-I alone [89] and Dkk-1 [94], with treatment response mainly to tocilizumab or TNFi. Notwithstanding these positive findings, the predictive

value of these markers remains modest, and concerns remain about their reproducibility. Moreover, the small cohort size and the different clinical outcomes currently hinder their routine use.

The analysis of two RCTs revealed conflicting results regarding the predictive utility of specific serum biomarkers, CXCL13 and ICAM1 [97, 99].

ICAM1 is a molecule involved in cell adhesion and inflammation; when elevated, it may indicate more severe inflammation and immune system activation [100]. Conversely, CXCL13 is a chemoattractant factor for B cells, generally associated with the formation of lymphoid follicles in lymphatic tissue [101] but also shown to be elevated in the inflamed synovium, where it can contribute to the formation of ectopic lymphoid structures. In one study [99], analyzing synovial tissue samples from 2 cohorts of 49 and 20 patients using a combination of global gene expression, histologic and cellular analyses, and analysis of gene expression data from two further publicly available RA cohorts, four distinct synovial phenotypes in RA were identified: lymphoid, myeloid, low inflammatory, and fibroid, each with unique gene expression signatures. Patients with higher baseline expression of synovial myeloid genes responded better to TNFi. Baseline serum levels of soluble ICAM1 and CXCL13 showed differential effects on clinical response to TNFi versus anti-IL-6R treatment. Patients with sICAM^{high}/CXCL13^{low} had a higher rate of ACR response to TNFi treatment compared to IL-6R inhibition, whereas individuals with sICAM^{low}CXCL13^{high} were more likely to respond to tocilizumab. Although interesting, the study used different cohorts and the absence of a validated cutoff to establish the levels of sICAM and CXCL13 limit the predictive value of the markers. In addition, these findings are in contrast with the ones reported in another retrospective analysis [97], involving patients with moderate-to-severe active RA, who didn't respond sufficiently to methotrexate. In this study serum specimens were examined at baseline and after treatment up to 24 weeks. Baseline levels of CXCL13 and sICAM-1 were examined to assess whether different biomarkers ratios could associate with clinical responses to sarilumab or adalimumab. While patients with CXCL13^{high}/sICAM-1^{high}, as well as those with CXCL13^{low}/sICAM-1^{low} exhibited more significant ACR50 responses with sarilumab compared to adalimumab, other combinations did not show predictability. In conclusion, conflicting findings regarding the predictive utility of specific serum biomarkers, such as CXCL13 and ICAM1, underline the need for further validation in independent cohorts. Additionally, the incorporation of serum biomarkers into predictive models may enhance their clinical utility and facilitate personalized treatment decisions in RA.

3.8 Predictive models based on synovial molecular signatures for treatment response to Tocilizumab or Rituximab, and refractoriness (fibroblast and ECM signature), have been reported (LoE: 1b). Several genes in synovia have been associated with response to bDMARDs; however, these observations originate from observational studies with relatively small sample sizes (LoE: 2b).

In recent years, the advancement in the molecular characterization of RA has led to considering synovia as the principal tissue to investigate in order to understand disease pathogenesis and treatment response. Indeed, an increasing body of evidence that the molecular mechanisms that lead to synovitis are not the same at the patient level. We included in the analysis 10 studies which investigated the role of genes, transcripts, cytokines, and chemokines as potential predictors of treatment response [99, 102-111]. Most of these articles were observational studies [102-109] while only four were RCTs [99, 103, 110, 111]; however, the overall number of patients enrolled in each study was small. Four studies analyzed the association between various molecules, including LT- α and TNF [102], CRP, and MMP3 [104] and MCP-1 and MIP-1b [105] and treatment with different bDMARD, particularly TNFis, but they failed to demonstrate any relationship. An observational study conducted on csDMARDs-IR patients highlighted the presence of 21 down- and 72 up-regulated synovial genes in responders to TNFis compared to non-responders [109] suggesting a different molecular expression pattern after treatment. So far, only one RCT examined directly the synovial inflammation [111]. The R4RA trial is the first biopsy-driven trial in which TNFi-non-responder patients were randomized to either rituximab or tocilizumab. Patients were stratified in B cell-rich and B cell poor according to the B cell count in the synovia through histology and molecular analysis. The study showed that patients classified as B cell-poor through RNA-sequencing were less likely to respond to rituximab compared to tocilizumab; however, the primary outcome was not reached when classifying the patients according to histology, suggesting the need for a deep molecular classification to better predict treatment response. An in-depth post-hoc analysis of the trial provided a predictive algorithm of treatment response to individual medication, while refractoriness was associated with a stromal-fibroblast signature [111]. Despite the potential of synovial biomarkers in guiding treatment decisions, challenges remain in translating research findings into clinical practice. Standardization of synovial tissue sampling and analysis methods, and validation in larger patient cohorts, are critical steps towards integrating synovial biomarkers into routine clinical care for RA patients.

4.0 Systemic lupus erythematosus

4.1 In terms of demographic characteristics rituximab seems more effective in African American and Hispanic people, ustekinumab in Caucasians while belimumab seems to be inefficacious in the black population (LoE: 2b). Respect to patients' clinical characteristics belimumab and atacicept have greater efficacy in patients with high disease activity (SELENA SLEDAI ≥ 10), whereas skin response to anifrolumab is higher in patients with a baseline CLASI ≥ 10 (LoE: 2b). Concerning laboratory features, belimumab and atacicept have higher efficacy in serologically active patients (high anti-dsDNA and/or low complement), anifrolumab in patients with high IFN gene signature at baseline and iberdomide in patients with high IFN gene signature or high Aiolos signature at baseline (LoE: 2b).

SLE is a multisystemic autoimmune disease that typically affects multiple organs. Different clinical subsets sustained by different underlying immunological abnormalities are being acknowledged in SLE [112], which may be likely to show different responses to given treatments. Several drugs are available in the pipeline for the treatment of different clinical manifestations, and, in recent years, two monoclonal antibodies, belimumab and anifrolumab, have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) specifically for the treatment of this condition. Nevertheless, the variability of the disease spectrum makes the treatment of SLE quite difficult, and, despite therapy, most patients experience frequent disease flares and accumulate organ damage. Since no drug has proven to be efficacious in all patients, the identification of clinical or laboratory features providing insights into susceptibility to different drugs is required for a personalized therapeutic approach. To address this issue, we performed a systematic literature review, retrieving a total 317 articles, of whom 38 were considered eligible (31 RCTs and 7 post-hoc analyses).

One of the first biologic therapies studied in SLE is rituximab (RTX), a chimeric monoclonal antibody that selectively targets CD20-positive B cells and is approved for the treatment of non-Hodgkin's lymphoma and RA [113-115]. The results of several small uncontrolled trials have suggested that RTX might have potential efficacy and be steroid sparing in SLE [116-125]. Very few data are available about the different response of subgroups of patients to RTX in RCTs. Indeed, when considering the efficacy of RTX in extrarenal SLE, only the EXPLORER trial performed a preplanned subgroup analysis demonstrating a possible ethnicity influence: while the trial failed to

demonstrate efficacy in the whole population, a beneficial effect of RTX on the primary endpoint (assessed using each of the 8 BILAG index organ system scores) was observed in the African American/Hispanic subgroup, while not in the other ethnic groups [126]. Belimumab (BLM) is a human immunoglobulin monoclonal antibody against B lymphocyte stimulator [127] a potent B cell survival factor associated with human SLE [128,129]. The safety and efficacy of intravenous BLM, at a dose of 10 mg/kg, as add-on therapy in patients with SLE was demonstrated in two large phase III RCTs, that led to its approval as first biological agent for the treatment of SLE by FDA and EMA [130-131]. Data from post hoc analyses of the BLISS 52 and BLISS 76 showed that serologically active disease (high anti-DNA titres, low C3/C4), high disease activity (SLEDAI 2k ≥ 10), concomitant prednisone and antimalarial treatment, and baseline prednisone > 7.5 mg/day were associated to a higher rate of SLE responder index (SRI)-4 response to BLM treatment [132-134]. Interestingly, a post-hoc analysis of the BLISS 52 and BLISS 76, showed that patients taking belimumab had a reduced cumulative dose of steroids at the end of the study, regardless baseline disease activity [135]. More recently the influence of serological activity on treatment efficacy was also confirmed for weekly subcutaneous BLM [136]. Interestingly, BLM seems to be less effective in the Black African ancestry: in the EMBRACE trial, which included 448 patients with self-identified Black race, Belimumab did not meet the primary endpoint of improvement in the SRI-4 SLEDAI-2K response rate [137]. However, improvements were observed especially in patients with high disease activity at baseline, suggesting that BLM might remain a suitable treatment option in Black patients. Atacicept, a fusion recombinant protein that inhibits BLyS and APRIL, has also shown to be more efficacious in patients with high disease activity (SLEDAI 2k ≥ 10 at baseline), high anti-dsDNA and low complement levels in the ADDRESS II phase 2 clinical trial [138].

Anifrolumab, an anti-IFN-1 receptor human monoclonal antibody, was recently approved by FDA and EMA for the treatment of SLE based on the results of the TULIP-2 trial. In the phase 2 [139] and phase 3 [140] RCT patients with baseline high IFN signature showed greater effect in terms reaching the primary endpoint respect to patients with low IFN-1 signature. Moreover, the CLASI response was higher in patients with high CLASI (≥ 10 points) at baseline, suggesting a higher efficacy of the drug in patient with moderate to severe cutaneous involvement.

Finally, the recent phase 2 trial of Iberdomide, a cereblon modulator promoting degradation of the transcription factors Ikaros and Aiolos, showed a better response in patients with higher IFN-1 signature and higher Aiolos signature [141].

4.2 Belimumab seems to have greater efficacy in patients with proliferative vs. membranous LN and on a background therapy with MMF (LoE: 2b). Belimumab seems to be more effective in LN patients of Black ancestry and those with a baseline proteinuria <3g/day (LoE: 2b). Voclosporin proved effective across all histological classes, including a clinically meaningful efficacy in class V (LoE: 2b). Obinotuzumab seems to be more effective in class IV LN (LoE: 2b).

Lupus nephritis (LN) is still impacting the long-term prognosis of SLE patients, leading to renal failure in up to 20% of cases [142]. Until recently, RCTs on LN were burdened with unsucccess, preventing drugs such as RTX from being licensed for use in LN [143], despite being included in the international recommendations for LN since a long time. In the last decade, promising molecules have arisen and more suitable RCT designs have been employed which highlighted the additional benefit of a novel add-on treatment over standard of care (SoC) alone. Overall, 7 RCTs and 1 post-hoc analysis were retrieved in our SLR on this topic.

BLM (anti-BLyS), already licensed for non-renal SLE in 2011, has shown increased benefit when added to SoC during the initial treatment of LN, leading to significantly increased renal response rates (+11%) in the drug vs. placebo arm in the phase 3 BLISS-LN trial [144]. This RCT was undertaken due to a strong immunological rationale for early belimumab use in SLE, also considering a previous post-hoc analysis on phase 3 RCTs for belimumab where data on patients with concomitant renal involvement were analyzed [145]. Despite not reaching statistical significance, the analysis showed increased efficacy of belimumab in patients with renal activity, ongoing MMF treatment and active serology, suggesting that a subgroup of patients could particularly benefit from an early combination treatment with belimumab. Consistently, the BLISS-LN RCT assessing renal response in patients receiving belimumab + Soc vs. SoC alone was successful, showing an even greater response rate in patients with proliferative LN, subnephrotic proteinuria and preferentially receiving mycophenolate over cyclophosphamide [144,146]. Combination treatment with belimumab was also associated with flare reduction and preserved glomerular filtration rate (GFR) in the long term.

The calcineurin inhibitor voclosporin was successful in phase 2 and 3 RCTs comparing voclosporin plus SoC vs. SoC alone in LN [147, 148], showing a significant improvement in renal response and preservation of renal function in the long term in the drug arm, notwithstanding a temporary drop in GFR within the first four weeks of treatment.

Similarly to belimumab, the addition of voclosporin was more effective on a mycophenolate background. Despite the RCT was not specifically designed for this purpose, voclosporin showed also a + 10% renal response in patients with membranous classes of LN versus placebo. Interestingly, belimumab was less effective among Black patients with LN, while voclosporin obtained better response rates among non-white races in the AURORA trial.

Data on anti-IFNAR anifrolumab in LN are still scarce, as the phase 2 TULIP-LN failed in reaching the primary endpoint. Nevertheless, a phase 3 RCT of anifrolumab in LN is ongoing, acknowledging the immunological rationale and according to favorable data from TULIP-LN RCT showing renal efficacy for the intensified anifrolumab regimen in proliferative LN [149]. The new anti-CD20 obinutuzumab is in the pipeline for LN, having succeeded in the phase 2 RCT and being currently under investigation in a phase 3 (NCT04221477). In prespecified subgroup analyses of the phase 2 trial, the benefit of obinutuzumab over placebo at 104 weeks was greatest among patients with class IV (as compared with class III) LN on renal biopsy.

Overall, current data from RCTs in LN showed superiority of early combination treatment in LN, where a novel drug is added to SoC in the very initial treatment of LN. Such approach led to improved renal response and renal survival and allowed a quick and safe steroid tapering in the drug arms. The choice of which drug to be added first should be refined considering histology (proliferative vs. membranous), proteinuria levels, baseline renal function and eventually patient ethnicity, in order to increase the a priori chances of response. Deeper understanding and targeting of underlying molecular pathways resulting in clinical and histological features will likely improve the personalization of treatment.

5.0 Sjogren disease

5.1 Stratification for salivary flow rate at baseline should be evaluated for inclusion into RCTs. The salivary flow rate improves following treatment with drugs with different mechanisms of action (RTX, RTX and belimumab, abatacept, HCQ, HCQ and leflunomide) (LoE: 1b). In 2 open label studies baseline salivary flow rate predicted improvement in salivary function (LoE: 2b).

Different studies on RTX, from 2005, with different design, both open label and RCTs showed an increase in salivary flow rate after this treatment in SjD.

In a small open label conducted by Meijer et al. in 2009, 5 patients, who underwent retreatment with RTX in the extend follow up, had an increase on the stimulated

submandibular/sublingual salivary flow at week 12, followed by a gradual decline to just above baseline at 48 weeks [150]. In the first RCT conducted by Meijer et al. in 2010, 20 patients were treated with intravenous (IV) infusions of 1000 mg of RTX and 10 patients were treated with IV infusions of placebo on days 1 and 15 [151]. The primary end point was met, in fact the stimulated whole saliva flow rate significantly improved in the RTX group ($p = 0.018$ at week 5 and $p = 0.004$ at week 12, versus baseline), while in the placebo group these values significantly decreased from baseline. A significant difference in the mean change from baseline to week 12 in the stimulated whole saliva flow rate was found between treated and untreated patients ($p=0.038$). The unstimulated whole saliva flow rate and the submandibular/sublingual flow rate also significantly increased from baseline in the rituximab group [151]. In another open label study conducted by Carubbi et al. in 2013, RTX was able to significantly increase the unstimulated salivary flow from week 12 [152]. These studies suggest the value of selecting patients with residual salivary gland function for inclusion in clinical trials, in order to demonstrate an increase in salivary flow after treatment. In fact, in a small prospective, single-center, open-label phase II study, conducted by Pijpe et al. in 2005, 15 consecutive patients with early SjD ($n=8$) or MALT/SjD ($n=7$), were enrolled and treated with RTX and functional assessments. Fourteen patients completed the study [153]. Although no significant changes were seen in whole salivary flow, stimulated submandibular/sublingual salivary secretion increased significantly in patients with a stimulated salivary flow >0.10 ml/minute at baseline (in all patients with early SjD and 2 with MALT/ SjD). No changes were seen in patients with a stimulated salivary flow of <0.10 ml/minute at baseline (5 patients with MALT/SjD) [153].

RTX and BEL sequential treatment in a 68-week, phase II RCT, including 86 SjD patients, showed a trend toward a higher stimulated salivary flow at weeks 52 and 68 [154]. Patients were randomized to receive placebo, both subcutaneous BEL and RTX, or monotherapy with BEL or with RTX [154].

To evaluate the effectiveness and safety of abatacept (ABA) in SjD, a small open label study was conducted in 2019 by Machado et al. Eleven SjD patients were treated with ABA at day 1, 15, 29 and every 4 weeks. This study showed a statistically significant improvement in salivary flow from the baseline to 24 months ($p= 0.003$) [155].

As long as csDMARDs in SjD are concerned, in a small single center, open-label pilot study in 2010, 30 women with early SjD scheduled for HCQ treatment (400 mg daily) for 30 weeks of treatment. The uSFR increased throughout the HCQ treatment, and

the amount of increase was significant at each time point (6, 12, 18, 24, 30 week) [156].

In a subsequent RCT, conducted by van Der Heiden et al. in 2020, patients were randomly assigned (2:1) to receive leflunomide (LEF) 20 mg and hydroxychloroquine 400 mg daily, or placebo for 24 weeks [157]. A significant increase in UWS was observed in patients receiving HCQ and LEF compared to placebo after 24 weeks of treatment ($p=0.014$) [157].

5.2 Although these parameters have not been evaluated as predictors of clinical response, baseline levels of RF, IgG should be considered as stratification tool in RCTs. The decrease of RF and IgG serum level have been consistently reported following treatment with drugs with diverse mechanisms of action (RTX, RTX and belimumab, abatacept, HCQ and leflunomide) (LoE: 1b).

Different open label studies and RCTs showed a decrease in the levels of IgG and RF after RTX treatment. In particular, in a small prospective, single-center, open-label phase II study, conducted by Pijpe et al. in 2005, B cell depletion was accompanied by a significant decrease in IgM-RF levels at week 5 in patients with MALT/ SjD. Instead, IgG, IgA, IgM, and β 2-microglobulin levels did not change in either group of patients [153]. In another double blind, placebo-controlled, randomized pilot study, conducted by Dass et al. in 2008, showed a significant difference in the reduction of RF between the two groups at 6 months (45 vs 0, RTX vs placebo, $p=0.05$) but no significant change was observed in immunoglobulin levels or titers of other antibodies [158]. In the extended follow-up in 2009, RTX retreatment of the patients with early SjD, 48-week follow-up data were available: retreatment had a significant effect on B cells (numbers, populations?) and levels of IgM-RF [150]. Furthermore, Meijer et al. consistently observed significantly reduced levels of RF 5-36 weeks after RTX treatment compared to the baseline [151]. These findings were supported by several other investigators [159-161]. Two studies indicated that increasing levels of RF during B cells repopulation may predict a disease relapse [160-161]. Regarding IgG levels, a large RCT by Devauchelle-Pensec et al. [162], and two small studies, conducted by Meijer et al. and Meiners et al. showed a significant reduction in the total serum IgG level 24 weeks after treatment or later [150,159], RTX and BEL, in a 68-week, phase II RCT, including 86 patients with active SjD, showed a significant trend toward a reduction in both IgG and RF levels in the BEL + RTX group when compared to placebo [154]. In a phase III, double-blind, placebo-controlled trial, conducted by Baer et al. in 2011, eligible patients

with active SjD were randomized 1:1 to receive either weekly sc ABA 125 mg or placebo for 169 days [163]. Of 12 selected disease-relevant laboratory parameters and biomarkers, mean change in IgG IgM-RF serum levels was significantly different between the ABA and placebo group at day 169, while ABA treatment did not result in significant clinical efficacy compared with placebo in patients with moderate-to-severe SjD, despite evidence of biological activity [163].

As far as HCQ and LEF are concerned, in an RCT, conducted by van Der Heiden et al. in 2020, patients were randomly assigned (2:1) to receive LEF 20 mg and HCQ 400 mg daily or placebo for 24 weeks. A significant decrease in serum IgG and IgM RF levels was observed in patients receiving HCQ and LEF compared to placebo after 24 weeks of treatment: serum IgG ($p = 0.0013$), IgM RF ($p=0.017$) [157].

5.3 Selection of patients based on activity level in the articular, constitutional, lymphadenopathy, glandular and biological ESSDAI domains is advisable in RCTs. Improvement in joint, constitutional, glandular, lymphadenopathy, and biological ESSDAI domains has been reported following treatment with drugs with diverse mechanisms of action (iscalimab, ianalumab, HCQ and leflunomide) (LoE: 1c).

In the multicentre, randomized, double-blind, placebo-controlled trial of the anti-CD40 antibody iscalimab, conducted on 82 patient who were randomly assigned to receive either 3 mg/kg doses of iscalimab, IV 10 mg/kg doses of iscalimab, or placebo ($n=4$), and in cohort 2, 32 patients were randomly assigned to receive either, for 12 weeks. IV treatment with iscalimab resulted in a mean reduction of 5.21 points (95% CI 0.96–9.46; one-sided $p=0.0090$) in ESSDAI score compared with placebo. There was no significant difference in ESSDAI score between SC iscalimab and placebo [164].

A post-hoc analysis showed improvements in clinical ESSDAI (ESSDAI without the biological domain) at week 12 for IV iscalimab compared with placebo, with a reported reduction of 6.10 points (1.08 to 11.11) [164]. The articular domain had the greatest reduction in ESSDAI score at week 12, even as articular ESSDAI domain was the most severely affected domain at baseline. Another smaller RCT investigated the effectiveness of ianalumab, a monoclonal antibody that blocks the B-cell activating factor (BAFF) receptor, in 27 SjD patients. The study showed that ESSDAI scores at the end of the study in patients treated with 10 mg/kg ianalumab remained at reduced levels achieved over the 24-week blinded period. Furthermore, the evaluation of individual ESSDAI domains revealed that most improvement was in the articular domain with ianalumab treatment [165]. A small single-centre phase IIA RCT on 29 SjD patients

treated with the combination therapy LEF/HCQ (n=21) or placebo (n=8) showed a significant decrease in ESSDAI in favor of the LEF/HCQ group compared to placebo. From 0 to 24 weeks, the mean difference in ESSDAI score, adjusted for baseline values, in the leflunomide–hydroxychloroquine group compared with the placebo group was –4.35 points (95% CI –7.45 to –1.25, p=0.0078). This difference was mainly driven by the constitutional, biological articular, lymphadenopathy, and to a lesser extent the glandular domain of the ESSDAI [157].

6.0 Systemic sclerosis

Note: in this work, the SSc working group only included subgroup analysis based on treatment differences between the study arm vs. the placebo/control arm of RCTs. Simple inner-arm comparisons were not accepted.

6.1 We recommend background therapy to be allowed for RCTs investigating disease-modifying agents in SSc. Stratification and pre-specified analyses should be conducted (LoE: 2b).

In recent years, a growing number of RCTs on SSc allowed in their design background treatments considered standard of care, such as therapy with mycophenolate mofetil (MMF). The group agreed that this is a pragmatic, feasible, and ethically favorable design. In addition, there is evidence that subgroups with and without background treatment respond differentially to study drugs. For example, in the SENCISIS trial, which evaluated the efficacy of nintedanib in patients with interstitial lung disease (SSc-ILD), the background use of MMF or MTX was pre-defined as subgroups for statistical analysis [166]. The treatment response in the nintedanib and placebo groups showed heterogeneity based on background MMF use for some of the lung outcomes. The treatment difference was more prominent in MMF- patients than in MMF+ patients, as measured by achieving forced vital capacity improvement (FVC increase $\geq$ 3% predicted) at week 52. The odds ratio of treatment vs. placebo was 1.01 (95% CI 0.57 to 1.81) in the MMF+ group and 3.17 (1.63 to 6.16) in the MMF-group, subgroup heterogeneity P=0.011 [167]. At 100 weeks, the annual rate of decline in FVC (ml/year) differed numerically between MMF- and MMF+ patients with a treatment difference of 5.4 mL/year [95% CI –37.9 to 48.8] in MMF+ and 61.3mL/year [18.6 to 104.0] in MMF- patients, heterogeneity P=0.072 [168]. In addition, there were numerical differences in the primary outcome of annual FVC decline after 52 weeks between MMF- and MMF+ patients treated with nintedanib [167]. Similarly, a post-hoc stratification for previous

cyclophosphamide (CYC) therapy has been performed in RCTs on autologous hematopoietic stem cell transplant (aHSCT) [169]. The treatment difference between aHSCT vs. control (CYC) was significant in CYC naive patients but not significant in CYC pre-exposed patients, in terms of global rank composite score and event-free survival (survival without respiratory, renal, or cardiac failure) at 54 months. In other studies, such as the romilkimab trial for diffuse cutaneous SSc (dcSSc), the treatment effects for the primary endpoint mRSS were higher in patients taking background immunosuppressants, but there was no difference to placebo whether or not patients were taking background immunosuppressants [170]. Therefore, one should not assume that background therapy is always leading to different responses for any study drug, and this interaction needs to be analyzed in each individual scenario. Building on these notions, the group convened that background therapy should be included as stratification criteria and statistical analysis for treatment heterogeneity based on background therapy should be pre-specified.

6.2 We recommend that the severity of organ involvement (lung and skin) should be considered for stratification and pre-specified analyses in RCTs (LoE: 2b).

Disease severity may lead to different treatment responses, as seen in RCTs assessing the efficacy of romilkimab, riociguat, and CYC. In the romilkimab phase II trial for dcSSc, a statistically significant difference between treatment and placebo was observed in a pre-specified subgroup of patients with more severely affected skin at baseline (mRSS ≥ 15) [170]. Similarly, in the RISE-SSc trial, although treatment with riociguat did not show a significant change of mRSS at 52 weeks, a pre-specified subgroup analysis of patients with a higher baseline mRSS score between 17 and 22 reached numerically statistical significance for change in mRSS compared to baseline mRSS 10 to 16 [171]. In the same study, the severity of lung function impairment predicted a better response: in patients with baseline FVC 50-75% predicted compared to FVC over 75%, the mRSS change at 52 months was in favor of riociguat versus placebo with a nominal p-value < 0.05 . In the Scleroderma Lung Study 1 (SLS1) assessing the efficacy of CYC compared to placebo in SSc-ILD patients, a post hoc analysis showed that patients with baseline FVC $< 70\%$ predicted had a significantly greater absolute difference in adjusted 12-month FVC% predicted treated with CYC compared to placebo (4.62% higher FVC % predicted in the CYC group; $P=0.007$) [172]. Accordingly, baseline lung fibrosis assessed through a chest high-resolution CT (HRCT) scoring, the FIB_{max} score, significantly correlated with the placebo-adjusted change in

FVC% predicted at 18 months (mean correlation coefficient 4.94, $P=0.01$). In the subgroup of patients with higher FIB_{max} score of ≥ 3 ($\geq 50\%$ involvement of any lung region, by reticular changes as assessed with HRCT), the CYC effect was much greater, resulting in an 8.96% difference in the % predicted FVC between CYC and placebo [173].

6.3 We recommend molecular profiling of bio-samples and explorative analyses for treatment response (LoE: 3).

Several biomarkers have shown discriminating effects in SSc RCTs, although most were not statistically significant or tested for heterogeneity regarding treatment responses. Nevertheless, high-throughput approaches are expected to provide more insightful efficacy strata than selected biomarker studies. Inflammatory markers are a promising group for this purpose. In the tocilizumab phase 3 trial for inflammatory early dcSSc (the focuSSced trial), the difference between tocilizumab and placebo was significant in the secondary outcome of time to treatment failure (hazard ratio [HR] 0.58, 95% CI 0.34–0.98). However, this significance disappeared after adjusting for baseline serum IL-6 (HR 0.63, 95% CI 0.37–1.06) [174], indirectly implying an effect of baseline serum IL-6 baseline levels on treatment outcome. In the post hoc analysis of the SLS2 study, which compared CYC and MMF head-to-head in SSc-ILD, high CRP levels or high levels of serum interferon-inducible proteins significantly predicted better response to both CYC and MMF in FVC decline at month 12 and month 24 compared to lower levels [175]. Beyond inflammatory markers, the autoantibody profile is a candidate biomarker for efficacy stratification. For instance, in the RISE-SSc trial of riociguat for early dcSSc, patients with positive anti-RNA polymerase III antibodies (ARA) had a numerically better treatment difference between riociguat and placebo in terms of 52-week mRSS (difference in the least squares mean between riociguat and placebo was -10.5391 in ARA+ patients and 0.3005 in ARA- patients) [171].

7.0 Adult-onset Still's disease

7.1 The efficacy of bDMARDs has been suggested on both systemic and joint features of AOSD without life-threatening organ manifestations even in long standing disease. Study design of available RCTs on AOSD did not allow to demonstrate a significant effect of biologic DMARDs (LoE: 2b)

The treatment of AOSD is complex and varies from GCs to cs- and bDMARDs of different modes of action [176,177]. In severe or refractory AOSD patients, multiple pieces of

evidence have increasingly suggested the usefulness of bDMARDs [178-180]. In this context, some RCTs investigated the efficacy of bDMARDs in treating AOSD; TNF, anti-interleukin-1 (IL-1) and (IL-6) inhibitors were assessed [181-184]. Furthermore, the administration of recombinant IL-18 binding protein was also evaluated in this context [185].

Firstly, in a non-randomized trial, a partial efficacy of etanercept was reported in the treatment of AOSD patients with active arthritis. This 6-month study included patients with active arthritis who were non-responders to at least one csDMARD. The main results showed the partial benefit of etanercept in treating active arthritis and in controlling systemic features [181]. Additionally, another observational study identified a quite low maintenance rate of TNFi in general in AOSD [186]. Subsequently, many clinical studies evaluated the efficacy, GC-sparing effect, and safety of IL-1 inhibitors, both anakinra and canakinumab [187-189]. Concerning RCTs of these drugs, two studies are available. The efficacy of anakinra was partially shown in the treatment of AOSD patients characterized by joint involvement and systemic features than those randomized to csDMARDs. Although not significant, a larger percentage of patients receiving anakinra reached disease remission and reduced the concomitant GCs after 6 months [182]. More recently, a randomized controlled trial assessed the efficacy of canakinumab in AOSD patients with active joint involvement. The main results demonstrated a more pronounced 12 week-reduction of both DAS28 and CRP levels in patients randomized to canakinumab than those receiving placebo, although not significant [183]. However, it must be pointed out that these RCTs were prematurely discontinued, due to enrollment issues, thus impairing the analyses on the primary endpoints.

Among the pro-inflammatory mediators involved in AOSD pathogenesis, IL-18 is considered a relevant mechanistic contributor [190-192]. In this context, in a phase 2 RCT, the safety and preliminary efficacy of tadekinig alfa, a recombinant human IL-18 binding protein, was assessed. The study enrolled AOSD patients with fever or increased CRP levels, refractory to previous csDMARDs or GCs. Tadekinig alfa showed a good safety profile and a potential efficacy on both joint involvement and systemic features [185]. These findings were maintained in long-term [193].

In addition, the clinical usefulness of IL-6 inhibition is also reported in treating AOSD [194]. A RCT investigated the efficacy of tocilizumab in active AOSD patients, who were inadequate responders to GCs for at least 2 weeks considering joint involvement and systemic features. The main results showed the efficacy of tocilizumab compared to the

placebo group in both these manifestations, although the primary endpoint was not met probably due to the underpowered analysis [184].

All things considered, although available RCTs suggested the potential efficacy in treating AOSD patients, there are several limitations to be taken into account. Although the efficacy may be suggested on both systemic and joint features, AOSD patients without life-threatening organ manifestations and in long standing disease were mainly assessed. The strict enrollment criteria of these RCTs could not be fully representative of the disease clinical picture of AOSD patients. Furthermore, the available RCTs defined the clinical response by using different criteria, developing own “home-made” criteria, thus reducing the possibility to compare the main results. Therefore, these limitations contribute to make more difficult the determination of the optimal timing for treatment initiation and the potential benefits of early intervention, as observed in the juvenile disease counterpart [195,196]. In addition, although AOSD is a rare disease, another limitation of the available RCTs is the small sample size, resulting in limited statistical power and limiting the efficacy analysis. Finally, the lack of head-to-head comparisons among different bDMARDs may reduce the possibility of determining which drugs should be prioritized in the management of these patients.

7.2 Future RCTs should stratify patients with active systemic disease (e.g., with fever) or active arthritis without fever. Future RCTs should include patients with active disease shortly (less than 1 month) after the flare onset. Study endpoints should combine low disease activity based on validated disease activity score (including fever for systemic disease) and significant reduction or discontinuation of concomitant glucocorticoids (LoE: 5).

AOSD patients are characterized by highly heterogeneous clinical manifestations in challenging the diagnosis and, consequently, the management of the disease [197]. In this context, although different clinical subsets of AOSD could be proposed [198,199] characterized by distinct clinical manifestations, further investigations are required to fully elucidate these topics [200,201]. Moreover, the potential presence of distinct clinical endotypes of AOSD may suggest the existence of different pathogenetic mechanisms, response to therapies, and long-term outcomes [198-201]. Thus, to implement the patient stratification in RCTs for AOSD, a better definition of clinical subsets is needed, to better identify patients with prominent systemic features than those with a main joint disease, in the absence of fever. This distinction may lead to

more tailored management of these patients, also identifying potential predictors of treatment response in optimizing the long-term outcome.

In addition, there is no standardized clinical tool for accurately measuring the disease activity of AOSD patients and to define the remission. In the available RCTs, completely different definitions of clinical response are specifically developed and used limiting the comparison of the results and their generalization. These issues might further decrease the reproducibility and validity of derived findings about drug efficacy, reducing the possibility of obtaining robust data. Therefore, the choice of a validated disease activity score is of crucial importance in improving the management of AOSD patients. Specifically, the development of a validated disease activity score, including fever and other inflammatory signs and symptoms could help to accurately assess the disease burden and response to treatment. In fact, the findings from RCTs may be in contrast with the strong scientific rationale, which is behind these studies, of inhibiting such cytokines in AOSD and the effectiveness reported in “real-life” settings [202,203]. In addition, a combination of the disease activity assessment with the reduction or discontinuation of concomitant GCs, may provide another clinically relevant feature to be considered about the efficacy of the drugs. Finally, in RCTs conducted so far, a large majority of patients with a long-standing Still's disease were enrolled, with a minor proportion of newly diagnosed participants. In fact, although burdened by significant relevant long term side effects, GCs have a clear efficacy in a substantial percentage of AOSD patients [204], which may lead to their exclusion from clinical studies. Thus, in future RCTs, it could be of interest to enroll patients with active disease shortly (possibly less than 1 month) after the flare onset.

7.3 Specific RCTs are needed for some AOSD life-threatening complications:

MAS pathogenic studies identified additional targets potentially interesting to inhibit (e.g., IL-18 and IFN- γ); Lung involvement deserves more investigations to clarify the different pathogenic subtypes (e.g., ILD, PAP) in order to conduct RCTs (LoE: 5).

AOSD is a severe disease with a possible fatal evolution due to the occurrence of some life-threatening complications [205]. Among these, macrophage activation syndrome (MAS) and lung involvement appear to represent the most common conditions associated with a poor prognosis in these patients [206-209].

MAS is codified as a secondary form of hemophagocytic lymphohistiocytosis (HLH); it is characterized by continuous high fever, adenopathies, and hepatosplenomegaly, in association with peripheral blood cytopenias, intravascular coagulation, and a marked

hyperferritinemia [210,211]. The hemophagocytosis, macrophages engulfed with signs of active phagocytosis toward other haematopoietic cells, is considered the histological disease hallmark, usually observed in bone marrow and in reticuloendothelial organs [212,213]. MAS has been reported in up to 15% of AOSD patients and it is burdened by high mortality rate (between 10 and 41%) due to a multiorgan failure [214,215]. Underlying disease flare, infections, and administered drugs may possibly trigger MAS occurrence in these patients [210]. Concerning MAS management, supportive measures, possible elimination of trigger, and immunosuppressive therapies are needed [211]. In this context, an early recognition of MAS is essential for a timely administration of an appropriate treatment. High dosages of GCs are the first-line therapy, generally in association with cyclosporin A and/or IV immunoglobulins [216,217]. In more severe and/or non-responder patients, IL-1-inhibitors, mainly anakinra (also at higher dosages than those usually administered in non-complicated patients), may be considered [210,211]. Recently, in patients with severe active disease despite this therapeutic strategy, etoposide has shown to have some efficacy [218,219]. In addition, the administration of emapalumab, a monoclonal antibody against IFN- γ , has been recently proposed in primary HLH and MAS secondary to SJIA, with a good preliminary response in terms of remission and survival [220,221]. Finally, in extreme non-responder cases, allogeneic hematopoietic stem cell transplantation could be considered in MAS, based on the evidence that this therapeutic procedure has dramatically improved the outcomes in primary HLH patients [222].

Taking together these observations, specific designed RCTs are needed to improve the management of MAS, considering its difficult rapidly evolving clinical scenario and high mortality rate in AOSD patients.

Among possible life-threatening complications in AOSD, lung involvement has been increasingly detected in this context based on the evidence of the juvenile disease counterpart. Despite a subtle/mild clinical picture at the beginning, the prognosis of this complication is poor [223,224].

In the first description, the authors reported that parenchymal lung disease was related to unusual clinical features of systemic idiopathic juvenile arthritis (SJIA), including acute erythematous clubbing, atypical skin rash, a high frequency of anaphylactic reactions to tocilizumab, eosinophilia ferritin elevation, and significant lymphopenia. Concerning the CT imaging, septal thickening, involving the periphery of multiple lobes with or without ground-glass opacities was the most common recorded finding. Interestingly, pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia were

recorded, as pathological findings, in association with atypical features including regional involvement and concomitant vascular changes [223,224]. These findings were similarly shown in another cohort of patients with SJIA [223,224]. On these bases, lung involvement has been also investigated and reported in adult patients, paralleling what already observed in previous studies in the juvenile counterpart [207,208]. A heterogeneous spectrum of clinical and radiological manifestations has been reported so far [207-209,225]. In fact, interstitial lung disease (ILD), pulmonary alveolar proteinosis (PAP), and acute respiratory distress syndrome have been variously reported during AOSD. Different CT scan findings were reported in AOSD patients, which appeared to be not mutually exclusive in the same patient, thus further complicating the assessment of this manifestation [207-209,225]. As observed in pediatric patients, lung involvement was associated with a poor prognosis in AOSD, suggesting a careful evaluation of this feature which was frequently related with MAS occurrence [207,208]. Finally, data on specific targeted therapeutic strategies are presently lacking about the management of these patients. In particular, the emergence of lung involvement in AOSD has coincided with the introduction of inhibitors of IL-1 and IL-6, suggesting a potential contribution of drug exposure. In this context, two possible pathogenic explanations have been recently proposed, namely DRESS hypothesis and or cytokine plasticity hypothesis, in deregulating the immune response toward the occurrence of this life-threatening evolution [226]. Therefore, during AOSD, lung involvement is emerging as an additional feature of concern, which requires further investigations to better clarify different pathogenic subtypes (e.g., ILD, PAP), diverse clinical features, and therapies of this complication in adult patients.

7.8 Several biomarkers have been proposed for AOSD diagnosis and disease activity assessment (ferritin, IL-18, IFN- γ , S100 proteins). Available data (reliability issues, threshold inconsistencies) do not support their use in RCTs for patient stratification so far (LoE: 5).

Several biomarkers are still under investigation in AOSD, in confirming the diagnosis, predicting complications, and recommending specific therapies, although outnumbering the validation studies. Thus, mechanistic, clinical, and therapeutic biomarkers have been increasingly proposed in this context [190,227]. Multiple lines of evidence have suggested the assessment of ferritin, IL-18, IFN- γ and its induced-chemokines (mainly CXCL9, CXCL10), and S100 proteins in better characterizing AOSD patients.

In regard to the diagnosis, ferritin is undoubtedly the most studied biomarker in AOSD [228-233]. A typical 5-fold increase of ferritin levels results to be suggestive for the diagnosis of this disease [234,235]. Several studies confirmed the assessment of ferritin as diagnostic feature in AOSD, although different cut-offs were identified in evaluated cohorts [228-233].

More recently, the importance of IL-18 assessment has been also proposed in AOSD diagnosis [236-240]. Particularly, IL-18 was reported to be specifically increased in AOSD patients, both active and inactive, when compared with patients with other inflammatory diseases [236-240]. In addition, the assessment of both ferritin and IL-18 was also proposed in assessing the disease activity of AOSD patients. In fact, ferritin and IL-18 may be elevated during flares whereas may be reduced in remission paralleling with disease activity [241-245].

Furthermore, the role of S100 proteins has raised some interest in AOSD diagnosis [246,247]. An accurate discriminative ability of these proteins, mainly S100A12, S100A8/9, could be suggested in distinguishing AOSD patients than healthy controls [248-250].

The evaluation of new biomarkers has been increasingly proposed in improving a timely detection of the occurrence of MAS. In this context, the role of ferritin and IL-18 was evaluated [251-255]. Marked increases of these molecules were reported during MAS when compared with inactive patients [251-255]. However, to date, even in this case, there is no unique validated single threshold to clearly identify the occurrence of this complication.

In addition, based on the crucial pathogenic role of IFN- γ and its pathway in MAS development, some related molecules were assessed as possible biomarkers of this life-threatening complication [256-260]. Interestingly, higher IFN- γ levels were detected in patients with MAS than those without this complication [257,260]. Furthermore, high levels of IFN- γ -induced chemokines were shown in MAS patients in respect to active patients without this complication or those in remission [256].

Finally, concerning the role of biomarkers in the context of therapy response, at present conflicting data are available in AOSD patients. In fact, there is not a specific validation about their use in predicting response to treatment or in evaluating the drug efficacy, limiting a possible application in clinical practice [190,227].

All things considered, although these biomarkers could have a various clinical utility in AOSD, additional specific designed and powered studies are needed to fully clarify their role in managing these patients due to reliability issues and threshold inconsistencies.

8.0 Spondylarthritis

8.1 In PsA, nor upadacitinib neither tofacitinib has consistently shown higher efficacy when used in bDMARD-naïve patients compared to bDMARD-experienced ones (LoE: 2b).

The efficacy of Tofacitinib in Psoriatic Arthritis (PsA) was evaluated in two randomized, placebo-controlled, double-blind phase 3 trials: OPAL BROADEN and OPAL BEYOND. The first evaluated the activity of Tofacitinib in patients with active PsA who had previously had an inadequate response to at least one csDMARDs, while the second investigated the efficacy of the drug in patients with active PsA who had had an inadequate response to at least one TNFi [261,262]. As demonstrated in the OPAL BROADEN, ACR20 response rates at month 3 were 50% in the 5-mg tofacitinib group and 61% in the 10-mg tofacitinib group, as compared with 33% in the placebo group and 52% in the adalimumab group (active control) ($P=0.01$ for the comparison of the 5-mg dose with placebo; $P<0.001$ for the comparison of the 10-mg dose with placebo). The same trend was confirmed by the ACR50 response rates (at month 3), which were significantly higher in each tofacitinib group (28% in the 5-mg tofacitinib group and 40% in the 10-mg tofacitinib group) than in the placebo group (10%; $P<0.001$ for both comparisons), as were the rates of ACR70 response (17% in the 5-mg tofacitinib group and 14% in the 10-mg tofacitinib group, vs. 5% in the placebo group; $P = 0.004$ for the comparison of the 5-mg dose with placebo; $P = 0.02$ for the comparison of the 10-mg dose with placebo) [261]. Taking into consideration the efficacy of tofacitinib in bDMARD-naïve patients, it was further investigated whether the same response could be achieved for bio-experienced ones. As shown by the OPAL BEYOND, ACR20 response were 50% with the 5-mg dose of tofacitinib and 47% with the 10-mg dose of tofacitinib, as compared with 24% with placebo ($P<0.001$ for both comparisons); ACR50 response were 30% with the 5-mg dose of tofacitinib and 28% with the dose of 10-mg of tofacitinib, comparing with the 15% reached in the placebo group ($P=0.003$ and $P=0.007$, respectively) [262]. Taking all of these into account, tofacitinib, at the dose of 5 mg, does not have a consistently superiority when used in bDMARD-naïve patients compared to bio-experienced one.

The efficacy of upadacitinib in treating PsA was evaluated in two randomized, placebo-controlled, double-blind phase 3 trials: SELECT-PsA 1 and SELECT-PsA 2. The first evaluated the activity of upadacitinib in patients with active psoriatic arthritis who had previously had an inadequate response to at least one csDMARD, while the second

investigated the efficacy of the drug in patients with active PsA who had had an inadequate response or intolerance to at least one TNFi [263-265]. The SELECT-PsA 1 demonstrated that, at week 12, improvement in ACR20 was achieved with both upadacitinib 15mg and 30mg doses versus placebo (70.6%, 78.5%, 36.2% respectively; $p < 0.001$ for both upadacitinib arms vs placebo) compared to adalimumab (65.0%). At week 24, ACR20 response was achieved by the 73.4% in the upadacitinib 15mg group compared to placebo 45.2% and adalimumab 67.1% ($p < 0.001$) [263]. Moreover, improvements in ACR50 were observed with both upadacitinib 15 mg and 30mg doses versus placebo at week 12 (37.5%, 51.8% and 13.2% respectively, $p < 0.001$ for both upadacitinib arms vs placebo) compared to adalimumab (37.5%), and at week 24 (52.4%, 60.5% and 18.9% respectively, $p < 0.001$ for both upadacitinib arms vs placebo) compared to adalimumab (44.3%). The ACR70 was achieved at week 12 by the 15.6% in the upadacitinib 15mg group and the 25.3% in the upadacitinib 30mg group vs placebo 2.4%, $p < 0.001$ for both upadacitinib arms vs placebo), compared to adalimumab (13.8%). The similar trend was observed also at week 24 (28.7%, 36.4% and 5.2% respectively, $p < 0.001$ for both upadacitinib arms vs placebo) compared to adalimumab (22.6%). No significant differences were noted in the comparison of the 15-mg dose of upadacitinib with adalimumab for the ACR50 or ACR70 response at 12 weeks [263,264]. As shown by the SELECT-PsA 2, at week 12, significantly more patients achieved an ACR20 response in the upadacitinib 15 mg and 30 mg arms versus the placebo arm (56.9%, 63.8% and 24.1%, respectively; $p < 0.001$ for both upadacitinib arms vs placebo). Response rates for upadacitinib 15 mg and upadacitinib 30 mg were 44.9% and 64.8% in the subgroup of patients who had failed >1 biologic DMARD and 55.8% and 66.7% in the subgroup of patients that were on monotherapy; these responses were similar to results in the overall population. Additionally, improvements in ACR50 and ACR70 were observed with both upadacitinib 15 mg and 30mg doses versus placebo at week 12 (31.8%, 37.6% and 4.7% respectively for the ACR50; 8.5%, 16.5% and 0.5% respectively for the ACR70) [265]. At week 24, ACR20 response was achieved by the 59.2% in the upadacitinib 15 mg group and 61.5% in the upadacitinib 30mg group compared to placebo 20.3% ($p < 0.001$ for both upadacitinib arms vs placebo). Moreover, improvements in ACR50 and ACR70 were observed with both upadacitinib 15 mg and 30mg doses versus placebo at week 24 (36.2%, 38.4% and 9.4% respectively for the ACR50; 19.4%, 23.9 % and 0.9% respectively for the ACR70) [265].

8.2 In patients with Axial Spondylarthritis, the factors associated with better clinical response for both upadacitinib and tofacitinib are bDMARD-naïve status, high levels of CRP, and positive MRI for sacroiliac or spine oedema (LoE: 1b).

The efficacy of Tofacitinib in patients with Ankylosing Spondylitis (AS) was evaluated with a phase II and a phase III study. The phase III study demonstrated that, when stratified by bDMARD treatment history, ASAS20/ASAS40 response rates at week 16 remained numerically greater with tofacitinib versus placebo, and in both treatment groups response rates were numerically greater in patients who were bDMARD-naïve versus those with TNFi-IR or prior bDMARD use without IR [266]. The phase II study was a 16-week (12-week treatment, 4-week washout), multicentre, dose-ranging trial, which enrolled patients with active AS, aged ≥ 18 years, who fulfilled the modified New York (mNY) criteria for AS, confirmed by centralized reading of sacroiliac radiographs. Post hoc subanalyses were performed to identify whether baseline CRP or MRI status could affect the efficacy of the drug [267]. Subanalyses of this phase II study demonstrated that patients with high (≥ 0.287 mg/dL) baseline CRP had a larger treatment effect with all doses of tofacitinib versus placebo than those with low (< 0.287 mg/dL) baseline CRP, significant for tofacitinib 5mg twice daily (ASAS20 78.6 % vs 37.8% tofacitinib 5 mg twice daily vs placebo ($p < 0.001$); ASAS40 47.6% vs 16.2% ($p < 0.001$)). Moreover, for patients with positive baseline MRI (SPARCC SI joint cut-off ≥ 2 at baseline), greater treatment effect was observed with all doses of tofacitinib versus placebo; significant for tofacitinib 5 mg twice daily (ASAS20 87.5% vs 40.0% tofacitinib 5 mg twice daily vs placebo ($p < 0.001$); ASAS40 48.4% vs 20.0% ($p < 0.01$)) [267].

The efficacy of upadacitinib in non-radiographic axial spondylarthritis was evaluated with a phase III, multicentre, randomized, double-blind, placebo-controlled study (SELECT-AXIS2). Eligible adults had active non-radiographic axial spondylarthritis, with objective signs of inflammation based on MRI or elevated CRP and an inadequate response to non-steroidal anti-inflammatory drugs. Patients were randomly assigned (1:1) to receive oral upadacitinib 15 mg once daily or placebo using interactive response technology. Random treatment assignment was stratified by MRI inflammation in the sacroiliac joints and screening high-sensitivity CRP status (MRI-positive and C-reactive protein-positive, MRI-positive and C-reactive protein-negative, and MRI-negative and C-reactive protein-positive) and previous exposure to bDMARDs (yes vs no) [268]. This study demonstrated that, when stratified by bDMARD treatment history, ASAS40 response rates at week 14 remained numerically greater with upadacitinib versus

placebo, and in both treatment groups response rates were numerically greater in patients who were bDMARD-naïve versus those with TNFi-IR or prior bDMARD use without IR (ASAS40 51% with upadacitinib at 15mg QD vs 22% in the placebo group compared to ASAS40 33% with upadacitinib at 15mg QD vs 24% in the placebo group). Moreover, subgroup analysis of ASAS40 response at week 14 by MRI sacroiliitis and screening CRP status demonstrated that upadacitinib-treated patients in the high CRP/MRI positive subgroup had greater treatment effect at week 14 versus placebo compared with those who had neither (High CRP/MRI+ group ASAS40 58% with upadacitinib at 15mg QD compared to placebo 14%) [268].

8.3 In Axial Spondylarthritis, the combination of both high levels of CRP and positive MRI for sacroiliac or spine oedema seems to be associated with better response to upadacitinib and tofacitinib than these two factors independently (LoE: 2b).

Analysis of treatment effect (ASAS20 and ASAS40) by composite baseline CRP/MRI status in the phase II trial of Tofacitinib and in the phase III trial of upadacitinib, demonstrated that patients in the high CRP/MRI-positive subgroup had greater treatment effect at week 12 (for tofacitinib) and at week 14 (for upadacitinib) versus placebo compared with those with these two factors independently or who had neither [266-268].

8.4 In PsA and Axial Spondylarthritis, BMI does not seem to affect the efficacy of both Upadacitinib and Tofacitinib (LoE: 2b).

Obesity has been associated with more severe disease activity, inferior quality of life and higher burden of hospitalization in patients with Psoriasis and PsA. It is known that a higher body mass index (BMI) is a risk factor not only for the development of PsA, but it is related to higher disease activity and poorer response to therapy including bDMARDs and, in particular, TNFi [269-271]. In fact, population pharmacokinetic studies of different TNFi have consistently shown that high body weight is associated with accelerated clearance, resulting in lower trough concentrations [269,272]. Additionally, obesity, particularly visceral fat, independently contributes to higher systemic inflammatory state [269,273]. Despite this trend observed with TNFi, the therapeutic efficacy of upadacitinib and tofacitinib is not affected by the BMI, as demonstrated by the SELECT-PsA1 for upadacitinib (stratifying for BMI <25 or BMI>25 the Response Rate was similar for both groups) and by the OPAL BROADEN and OPAL

BEYOND, in which tofacitinib demonstrated greater efficacy than placebo in patients with PsA, regardless of baseline BMI [261-263].

8.5 In Psoriatic Arthritis, differently from adalimumab, upadacitinib seems to show a comparable efficacy in both women and men (LoE: 2b).

Several studies suggest that being female is associated with a lower rate of success in obtaining response status in PsA patients treated with TNFi. In fact, female sex was identified as a predictor of drug discontinuation and may constitute a predisposing risk factor for flare and therapeutic switches [274-275]. Despite these results with TNFi, the efficacy of upadacitinib in PsA was comparable in both women and men [263,264].

8.6 In Psoriatic Arthritis and Axial Spondylarthritis, available data on filgotinib and deucravacitinib do not support, at present, a patients' stratification with regard to therapeutic response (LoE: 3).

The therapeutic efficacy of filgotinib and deucravacitinib in PsA and spondylarthritis is, at present, a matter of debate. Two phase II clinical trials were performed for filgotinib, the EQUATOR for PsA and the TORTUGA for Ankylosing Spondylitis, and one phase II RCT for deucravacitinib in PsA, with promising outcomes [276,277]. The lack of other studies does not allow, at present, a patients' stratification in relation to therapeutic response [278,279].

9.0 Discussion

Inflammatory rheumatic diseases are heterogeneous conditions related to an aberrant immune response along a pathogenic spectrum in which two-end phenotypes, autoinflammatory and autoimmune, may be recognized [1-3]. As reported in Table 1, we provided an overview of the importance of patient stratification during these diseases in regard to therapies in improving their management; where available, we mainly focused on RCTs.

As per other contexts also in inflammatory rheumatic diseases, RCTs are considered instrumental in building the evidence-based medicine to treat these patients, randomly assigning alternative therapeutic interventions in populations enrolled according to specific inclusion/exclusion criteria. The main results of RCTs are usually the estimates of the average treatment effect on the study participants [280-282]. Although these estimates are of importance in delineating the clinical usability of a treatment, some treated patients may experience more or less benefit than the retrieved average

[280,281]. This is highlighted in the context of RCTs but also in “real-life” studies where the clinical heterogeneity could be also increased [283]. The resulting possible variation in retrieved effects is defined as heterogeneity of treatment effects [284,285]. The latter may be quantitative, in case of subgroup effects in the same direction as the average effect but varying in magnitude, or qualitative, when treatment effects are in different directions in different subgroups since the treatment may be beneficial in some subgroups whereas harmful in others [280-285]. This heterogeneity of treatment effects may be substantial and should be carefully addressed in the contextualization and generalization of RCTs and “real-life” study assessing the efficacy of therapies [286-288]. The most direct approach to account this issue could be the organization of “n-of-1” trials, which assign individual patients to receive alternative therapeutic interventions in a randomly predetermined sequence [289,290]. However, these are applicable to a relatively small subset of conditions and therapies since they are subject to random within-patient variability [291]. Another possibility to limit this heterogeneity may be the stratification of patients according to risk of disease-related adverse events. In addition, for hypothesis generating purposes, a careful examination of heterogeneity within RCTs may be performed by subgroup analyses [292,293]. The main limitation of this approach is that the real effects may be not fully evaluated due to the inadequate statistical power, and reported effects may be spurious because of the performance of multiple statistical tests and/or due to random intra-individual variability [294,295]. Taking together these observations, the importance of a better stratification and characterization of patients, in both RCTs and “real-life” studies, in regard to therapies is increasingly needed to improve their management and long-term outcomes [296-299]. However, it not always possible to fully overcome these issues in the assessment of treatment effects suggesting the importance of systematic synthesis of literature and Experts’ consensus. The latter may be considered as a “condensed” overview of clinical issues supported by relevant literature, drawing upon the collective expertise and providing a pathway for clinical management [300,301]. In fact, consensus statements are developed to provide guidance when information is evolving and standards of care are not clear yet. They may be described as “a snapshot in time”, developed during a period of change marked by gaps in clinical information [301,302]. These methods of consensus may thus provide the basis for decision-making and considered interventions when there is no specific evidence or when there are doubts about the applicability of evidence generated from different populations enrolled in RCTs but also evaluated in “real-life” settings [300-303].

In conclusion, in this work, we provided an overview of the importance of a better stratification and characterization of the clinical heterogeneity of patients with inflammatory rheumatic diseases identifying this point as crucial in improving the treatment of these patients. These observations may indeed provide the basis for further clinical studies on patient disease subsets to increase the rate of achievement of clinical remission by a more tailored management.

10.0 References

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Table 1. Statements and level of Evidence

Statements	LoE
<i>RA working group</i>	
Seropositivity (ACPA and/or RF) is associated with an earlier and better response to MTX-based conventional treatment strategy in patients with early rheumatoid arthritis.	2b
Seropositivity is associated with a more evident reduction of structural damage in rheumatoid arthritis patients under an aggressive, MTX-based, treatment strategy	2b
Seropositivity is associated with increased efficacy of non-TNFi bDMARDs, especially rituximab.	1a
Seropositivity is also associated with a better response to abatacept and appears to be associated with a better response to tofacitinib.	2b
Despite stratification based on definite age cut-off (e.g., >65 vs. < 65 years) is mostly unavailable, age analyzed as continuous variable does not affect response to MTX.	2b
Age of golimumab start (>65 years vs. ≤65 years) does not affect its efficacy, in patients with RA under the same dosage of MTX.	2b

Younger age, analyzed as a continuous variable, is associated with a better response to etanercept, but information about MTX dosage is not available.	2b
Several single nucleotide polymorphisms have been associated with response to bDMARDs; however, their use as predictive biomarkers for treatment response is limited, and the effect size is small.	1a
Various genes and miRNAs in peripheral blood have been associated with response to bDMARDs; however, these associations are derived from observational studies, indicating a small effect size and limited clinical utility as predictive biomarkers for treatment response.	2a
Several serum proteins (OPN, SAA, CXCL13, VICM) have been linked to response to bDMARDs; however, their predictive value for treatment response is limited, and the effect size is small.	2b/3
In post-hoc analysis of two RCTs, the CXCL13 to sICAM-1 ratio has been implicated in informing response to TNFi versus IL6-receptor inhibition, albeit with contradictory results.	2a
Predictive models based on synovial molecular signatures for treatment response to Tocilizumab or Rituximab, and refractoriness (fibroblast and ECM signature), have been reported.	1b
Several genes in synovia have been associated with response to bDMARDs; however, these observations originate from observational studies with relatively small sample sizes.	2b
<i><u>SLE working group</u></i>	
In terms of demographic characteristics rituximab seems more effective in African American and Hispanic people, ustekinumab in Caucasians while belimumab seems to be ineffective in the black population.	2b
Respect to patients' clinical characteristics belimumab and atacicept have greater efficacy in patients with high disease activity (SELENA SLEDAI ≥ 10), whereas skin response to anifrolumab is higher in patients with a baseline CLASI ≥ 10 .	2b
Concerning laboratory features, belimumab and atacicept have higher efficacy in serologically active patients (high anti-dsDNA and/or low complement), anifrolumab in patients with high IFN gene signature at baseline and iberdomide in patients with high IFN gene signature or high Aiolos signature at baseline.	2b
Belimumab seems to have greater efficacy in patients with proliferative vs. membranous LN and on a background therapy with MMF.	2b
Belimumab seems to be more effective in LN patients of Black ancestry and those with a baseline proteinuria $< 3\text{g/day}$.	2b
Voclosporin proved effective across all histological classes, including a clinically meaningful efficacy in class V.	2b
Obinotuzumab seems to be more effective in class IV LN.	2b

<i>SjD working group</i>	
The salivary flow rate improves following treatment with drugs with different mechanisms of action (RTX, RTX and belimumab, abatacept, HCQ, HCQ and leflunomide).	1b
In 2 open label studies baseline salivary flow rate predicted improvement in salivary function.	2b
The decrease of RF and IgG serum level have been consistently reported following treatment with drugs with diverse mechanisms of action (RTX, RTX and belimumab, abatacept, HCQ and leflunomide).	1b
Improvement in joint, constitutional, glandular, lymphadenopathy, and biological ESSDAI domains has been reported following treatment with drugs with diverse mechanisms of action (iscalimab, ianalumab, HCQ and leflunomide).	1c
<i>SSc working group</i>	
We recommend background therapy to be allowed for RCTs investigating disease-modifying agents in SSc. Stratification and pre-specified analyses should be conducted.	2b
We recommend that the severity of organ involvement (lung and skin) should be considered for stratification and pre-specified analyses in RCTs.	2b
We recommend molecular profiling of bio-samples and explorative analyses for treatment response.	3
<i>AOSD working group</i>	
The efficacy of bDMARDs has been suggested on both systemic and joint features of AOSD without life-threatening organ manifestations even in long standing disease. Study design of available RCTs on AOSD did not allow to demonstrate a significant effect of bDMARDs.	2b
Future RCTs should stratify patients with active systemic disease (e.g., with fever) or active arthritis without fever. Future RCTs should include patients with active disease shortly (less than 1 month) after the flare onset. Study endpoints should combine low disease activity based on validated disease activity score (including fever for systemic disease) and significant reduction or discontinuation of concomitant glucocorticoids.	5
Specific RCTs are needed for some AOSD life-threatening complications: MAS pathogenic studies identified additional targets potentially interesting to inhibit (e.g., IL-18 and IFN- γ); Lung involvement deserves more investigations to clarify the different pathogenic subtypes (e.g., ILD, PAP) in order to conduct RCTs.	5
Several biomarkers have been proposed for AOSD diagnosis and disease activity assessment (ferritin, IL-18, IFN- γ , S100 proteins). Available data (reliability issues, threshold inconsistencies) do not support their use in RCTs for patient stratification so far.	5

<i>SpA working group</i>	
In PsA, nor upadacitinib neither tofacitinib has consistently shown higher efficacy when used in bDMARD-naïve patients compared to bDMARD-experienced ones.	2b
In patients with Axial Spondylarthritis, the factors associated with better clinical response for both upadacitinib and tofacitinib are bio-naïve status, high levels of CRP, and positive MRI for sacroiliac or spine oedema.	1b
In Axial Spondylarthritis, the combination of both high levels of CRP and positive MRI for sacroiliac or spine oedema seems to be associated with better response to upadacitinib and tofacitinib than these two factors independently.	2b
In PsA and Axial Spondylarthritis, BMI does not seem to affect the efficacy of both upadacitinib and tofacitinib.	2b
In PsA, differently from adalimumab, upadacitinib seems to show a comparable efficacy in both women and men.	2b
In PsA and Axial Spondylarthritis, available data on filgotinib and deucravacitinib do not support, at present, a patients' stratification with regard to therapeutic response.	3

Declarations

-Ethics approval and consent to participate:

Not applicable, this is a review of published evidence.

-Consent for publication:

Not applicable, all the patients' data are de-identified.

-Availability of data and material:

All data relevant to the review are included in the article.

-Competing interests:

The authors declare that they have no conflicts of interest for this work.

-Funding:

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-Authors' contributions:

All authors made substantial contributions to the conception or design of the work, the acquisition and interpretation of data. All authors contributed to the critical review and revision of the manuscript and approved the final version. All the authors agreed to be accountable for all aspects of the work.

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