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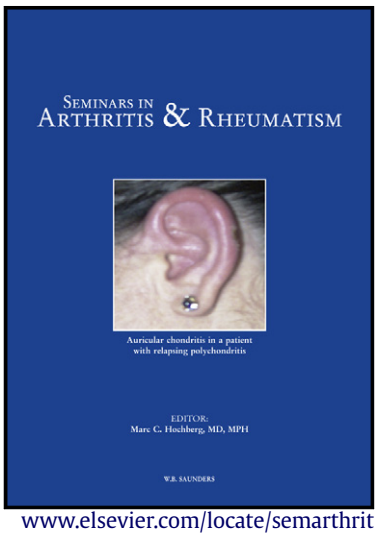

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Fabrizio Cantini, Laura Niccoli, Carlotta Nannini, Emanuele Cassarà, Olga Kaloudi, Ennio Giulio Favalli, Andrea Becciolini, Biggioggero Martina, Maurizio Benucci, Francesca Li Gobbi, Valentina Grossi, Maria Infantino, Francesca Meacci, Mariangela Manfredi, Serena Guiducci, Silvia Bellando-Randone, Marco Matucci-Cerinic, Rosario Foti, Marcella Di Gangi, Marta Mosca, Chiara Tani, Fabrizio Palmieri, Delia Goletti, On behalf of the Italian board for the TAilored BIOlogic therapy (ITABIO) members: Fabrizio Cantini

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Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis and psoriatic arthritis.

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Abstract.

Objective. A multidisciplinary expert panel, the Italian board for the TAilored BIOlogic therapy (ITABIO), was constituted to formulate evidence-based decisional statements for the first-line tailored biologic therapy in patient with rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA).

Methods.

Systematic review of the literature to identify English-language articles on the variables influencing the first-line biologic choice, including the efficacy and safety of the drug, the route of administration, the availability of response predictor biomarkers, the need of monotherapy, the patient socio-economic status, lifestyle, cultural level, personality, fertility and childbearing potential in women, the presence of comorbidities, the host-related risk factors for infection and latent tuberculosis infection (LTBI) reactivation, the cardiovascular (CV) risk, and costs.

Results. Some variables, including the patients' preference, the indication for anti-TNF monotherapy in potential childbearing women, and the intravenous route with dose titration in obese subjects resulted valid for all the three rheumatic conditions. Further, evidence of a better cost-effectiveness profile for etanercept (ETN) and biosimilar infliximab (IFX) in RA was found. Any biologic may be employed in absence of choice driving factors in RA. Otherwise, a high infection risk or LTBI positivity drive the choice toward abatacept (ABA), tocilizumab (TCZ), or ETN. TCZ should be the first choice if monotherapy is required. High rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) titers should drive the choice toward TCZ or ABA, while in patients at high CVD risk anti-TNF choice, with preference for ETN, seems appropriate. Presence of anterior uveitis or inflammatory bowel disease drives the choice to monoclonal antibody anti-TNFs (MoAb anti-TNFs). In PsA, ustekinumab (UTK), and to a lesser extent ETN, represents the first choice in patients at high infection and TB risk. Anti-TNFs or UTK choice is

guided by skin or articular disease severity, enthesitis, and dactylitis, whereas ETN should be preferred if metabolic syndrome or high CV risk complicate PsA.

Conclusion. Taking in account of multiple choice driving variables, first-line biologic therapy may be optimized in patients with RA, SpA, and PsA.

Keywords. Biologics, anti-TNF, tailored therapy, rheumatoid arthritis, spondyloarthritis, psoriatic arthritis.

Conflict of interest. All Authors declare no conflicts of interest.

1.0. Introduction.

To date, eleven biologic drugs have been licensed for the treatment of inflammatory rheumatic disorders such as rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA). Available biologics are characterized by a different pharmacological activity targeted on different levels of immune response, including interleukin-6 inhibitor tocilizumab (TCZ), anti-CD20 rituximab (RTX), anti-interleukin-1 anakinra (ANK), anti-CD28 abatacept (ABA), anti-IL12-23 ustekinumab (UTK), and anti-tumor necrosis factor alpha agents (anti-TNFs) adalimumab (ADA), etanercept (ETN), infliximab (IFX), golimumab (GOL), certolizumab pegol (CTP), and, limited to Europe, infliximab biosimilar (bio-IFX). RTX has been licensed as second-line therapy in RA patients failing the first biologic. All eleven biologics have been approved for the treatment of RA, while only the anti-TNFs can be employed in patients with SpA including ankylosing spondylitis (AS), non-radiographic axial SpA (n-rx-AxSpA), inflammatory bowel disorders-associated SpA (IBD-SpA). In addition to anti-TNF-targeted biologics, UTK has obtained the approval for the treatment of patients with (PsA).

Randomized clinical trials (RCTs) provide relevant data on the efficacy and safety of biologics, but, due to the study design, the patient selection, and the paucity of head to head studies, do not offer practical indication for a tailored therapy.

Several sets of recommendations/guidelines, including those of the American College of Rheumatology [1], European League Against Rheumatism [2]), Assessment of SpondyloArthritis international Society (ASAS) [3], Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [4], and of National scientific Societies from different countries, ensure the appropriate selection of patients requiring biologics therapy, but do not include indication for the optimization of therapy in the single patient. Indeed, in clinical practice, several variables may influence the biologic choice, including the efficacy and safety of the drug, the route of administration, the availability of biomarkers of response, the need for monotherapy, the characteristic of the patient in terms of working and socio-economic status, lifestyle, cultural level, personality, fertility and childbearing potential, the presence of comorbidities, the host-related risk factors for infection and latent tuberculosis infection (LTBI) reactivation, the cardiovascular (CV) risk, and cost.

Many of these variables have been singularly analyzed in different reports, but to the best of our knowledge, a comprehensive review of the factors impacting with the biologic choice and the proposal of a decisional algorithm for the correct therapeutic approach in the single patient are not available.

A multidisciplinary task force, the Italian board for the TAilored BIOlogic therapy (ITABIO), including specialists in rheumatology, infectious diseases, and immunology, was constituted to perform a review of the literature on the existing evidence on the variables conditioning the biologic choice, and to provide an evidence-based decisional tree for the tailored biologic therapy in patient with RA, SpA, and PsA.

2.0. Objective.

To provide appropriate statements and an evidence-based decisional tree for the tailoring of first-line biologic therapy in patients with RA, SpA, and PsA.

3.0.*Methods*

A multidisciplinary expert panel, the Italian board for the TAilored BIOlogic therapy (ITABIO), including specialists in rheumatology (MB, FC, EF, RF, SG, LN), infectious diseases (DG), and, immunology (MM), was constituted to review the literature on the existing evidence on the different variables influencing the biologic choice in patient with RA, AS, n-rx-AxSpA, and PsA. ITABIO group spontaneously developed in January 2015 when all members agreed that current guidelines/recommendations do not fully cover the biologic choice variables, and consequently decided to make an effort to provide practical indications for biologic prescribers. Each member separately developed and shared by e-mail a single topic, and finally all members met to examine, discuss, assemble the single elaborates, and to draw up the final manuscript. No funding source was available. The following topics were analyzed: disease severity, biologic efficacy and safety, monotherapy biologic choice, response predictors including biomarkers, extra-articular manifestations, comorbidities, fertility, childbearing potential, pregnancy, infection, LTBI reactivation, cardiovascular and malignancy risk, interval and route of administration, patient's preference, factor influencing the adherence to therapy. Taking in account the emerging evidence on the different factors, appropriate statements and decisional trees useful to tailor the biologic choice to the single patient were formulated.

3.1.Literature search.

The literature review was made using PubMed database to identify English-language articles related to the previously mentioned topics. Data were extracted from available recommendations, systematic reviews and meta-analyses, national registries of biologics, national healthcare databases, and post-marketing surveys. When these source data were not available for specific topics, the evidence was derived from open-label studies on variable sample-size clinical series.

The following drugs were investigated: IFX, bio-IFX, ETN, ADA, GOL, CTP, RTX, TCZ, ANK, ABA, UTK. The research was performed by crossing the single drug name with the following key terms: RA, SpA, PsA, efficacy, safety, monotherapy, response predictors, biomarkers, LTBI,

infections, tuberculosis (TB), comorbidities, cardiovascular risk, atherosclerosis, fertility, pregnancy, route of administration, patient's preference, adherence.

The literature review was extended to October 3, 2015.

4.0. *Results.*

4.1 *Efficacy of biologics in RA.*

The clinical efficacy of available biologic agents has been indirectly compared in several systematic reviews and meta-analyses, with controversial results depending on the different methodology applied and RCTs included in the analysis. ANK has been demonstrated to be less effective compared to other biologics in achieving both ACR20 and ACR50 response in at least 2 different studies [5,6]. Salliot et al. [7] found anti-TNFs as a group to be more effective than both RTX and ABA, and TCZ more effective than ABA, whereas Bergman et al. [8] reported that TCZ provided better results than both anti-TNFs and ABA in achieving ACR70 response. The comparative effect of biologics on functional status has been demonstrated to be similar in a meta-analysis by Callhoff et al. [9], whereas Barra et al. [10] found a lower effect on Health Assessment Questionnaire (HAQ) score in ABA, TCZ and IFX trials compared to other biologics. A comparative analysis based on the calculation of number needed to treat (NNT) demonstrated all biologics to have approximately the same efficacy in both clinical and radiographic response [11]. Moreover, a meta-analysis of biologic drug efficacy in preventing radiographic progression failed to identify significant differences among biological agents because of the huge heterogeneity in RCT baseline population characteristics [12]. In the ATTEST trial [13], ABA and IFX have been indirectly compared against the same comparator group, showing no relevant difference in EULAR and ACR response. More recently, a direct head-to-head comparison of subcutaneous ABA and ADA in patients with active disease despite methotrexate (MTX) revealed very similar clinical efficacy on symptom control and radiographic progression inhibition [14]. Finally, the PLANETRA trial has confirmed the non-inferiority of the first biosimilar drug of IFX (CT-P13) compared with IFX originator [15]. Therefore, considering overall results coming from direct and indirect comparative studies and with the only exception of

low ANK effectiveness, no preference of one over another biological agent should be expressed in terms of efficacy on clinical response, damage progression, and functional status.

The majority of RCTs evaluating the efficacy of biologic agents in refractory RA included patients with high disease activity [16-23]. In the CERTAIN trial [24], the only RCT focused on low to moderate (DAS28<5.1) RA patients, CZP in association with MTX showed a significantly better response compared to MTX in achieving clinical remission. Similarly, in a post-hoc analysis of the TEMPO trial, ETN treated RA patients with moderate disease were more likely to reach a lower disease activity state compared with those with higher disease activity [25]. However, to date no comparative analyses on the efficacy of biological drugs in the treatment of low to moderate RA have been published yet. Thus, baseline disease activity may not be considered as a driver for choosing the first biologic agent in clinical practice.

To date, no clear evidence on the efficacy of the different biologics in patients with RA complicated by vasculitis or pulmonary interstitial disease is available.

It may be postulated that the different mechanism of action (targeting cytokines or cell surface antigens) or the different route of administration may influence the time to response of biological agents. However, available data coming from observational or head-to-head comparative studies seem to demonstrated no significant difference in the kinetics of clinical effect of available biologic drugs [14,26].

The long-term efficacy of biologics may be better evaluated by data coming from large population-based national registries rather than open-label extension of RCTs. Thus, many studies from European and US biologic drug registries have provided data about drug retention in RA, also comparing in some cases the relative persistence of IFX, ADA, and ETN with controversial results. A French database [27]), the DREAM [28] and the RADIUS [29] registries showed no significant difference in drug survival among the anti-TNFs. Only the CORRONA registry [30] and insurance claims databases [26,31] found IFX to have a better persistence compared with both ETN and ADA, whereas 3 European registries (SCQM-RA, MonitorNet, and the Hellenic Registry of Biologics)

reported the opposite [32-34]. Other European observational studies confirmed ETN as having the highest long-term retention rate [35-40].

To date, no data are still available about long-term survival on treatment of RA patients treated with CZP or GOL, and reports on ABA and TCZ drug retention are often limited to anti-TNF insufficient responder rather than biologic naïve patients [41,42]. An observational study from the CORRONA registry showed a similar 2-year survival on treatment of ABA and anti-TNFs as first-line biologic drugs [43]. Similarly, no difference in 4-year drug persistence of first-line TCZ compared with anti-TNFs was found in the CABUKI registry [44]. However, a high TCZ discontinuation rate of 39% over a 3-year and 5-year follow-up period was observed in two recently published studies [45,46]. In conclusion, ETN seems to have the longest drug retention among anti-TNF agents, whereas insufficient data are still available regarding biologic agents with other mechanisms of action.

4.2. B*iologic choice in SpA and PsA.*

The SpA complex encompasses several entities including AS, non-rx Ax-SpA, IBD-associated SpA and PsA. Anti-TNF monotherapy after NSAID failure constitute the only validated biologic therapy for AS, non-Rx Ax-SpA, and IBD-associated SpA [3], while, according to GRAPPA recommendations [4], patients with peripheral PsA resistant to traditional disease modifying anti-rheumatic drugs (DMARDs) might be treated with anti-TNF or UTK [47].

In absence of head to head trials, the efficacy ADA, ETN, IFX, bio-IFX, GOL, and CTP for the treatment of AS, non-rx-Ax SpA has been evaluated by indirect comparison in several systematic reviews and meta-analyses [48-52]. Overall, no significant differences resulted, although a trend toward a better efficacy of IFX and bio-IFX in AS was recorded [49-51]. Of note, CTP resulted rapidly effective, probably due to the drug loading dose, in patients with non-rx Ax-SpA, with a significant difference in clinical response at first week of treatment as compared to control group[53]. Hence, limited to the efficacy, a slight preference for IFX or bio-IFX when starting to treat patients with AS might represent the better option. However, this option may be applied

depending on the country where clinicians are practicing, because, to date, bio-IFX has not been licensed in several countries, including the USA.

Regarding the safety, no significant differences have been observed among anti-TNF drugs, though a trend toward a better safety profile of ETN in terms of infection and TB risk resulted from systematic reviews, meta-analyses, and national registries of biologics [54-58].

However, beyond the efficacy and safety, the anti-TNF choice is driven by other variables examined in the present paper. Of note, considering that SpA occur at a lower age with respect to RA and PsA, the risk of pregnancy is higher and anti-TNFs with a shorter half-life are advisable to treat potential childbearing women.

Extra-articular manifestations in SpA such as acute anterior uveitis (AAU), and inflammatory bowel disease (IBD) have an important decisional impact because only monoclonal antibody anti-TNFs (MoAb anti-TNFs) are effective on these features [59,60]. Hence, unless in presence of other contraindication, MoAb anti-TNFs represent the better first-line choice for patients with SpA, especially if we consider that the articular manifestations may precede the onset of AAU or IBD [61].

PsA occurs in three main clinical patterns including peripheral, axial, and mixed, often complicated by dactylitis, enthesitis, and AAU [62]. Anti-TNFs are recommended in peripheral PsA patients failing traditional disease modifying anti-rheumatic drugs (tDMARDs) [4], while patients with axial involvement should be managed following the ASAS/EULAR recommendations for axial SpA [3]. Recently, UTK has been added to the therapeutic scenario of peripheral PsA, due to its efficacy on articular and skin features of the disease, while a weaker evidence of efficacy on axial manifestations resulted [47]. Data from RCTs and meta-analyses show a higher efficacy of UTK in terms of PASI75 response in the treatment of psoriasis compared to anti-TNFs, while UTK seems to have a lower efficacy on peripheral arthritis in terms of ACR20,50, 70 response criteria [63,64]. No data are available on the efficacy of UTK in AAU, while the drug, together with CTP and IFX, seems to have the greatest effect size in patients with dactylitis [65]. Clinical trials of UTK have

shown an excellent safety profile as regards infections, with no recorded cases of LTBI reactivation [66].

Two recent population based studies evidenced that PsA is associated with a higher risk of cardiovascular ischemic events (CVEs) as compared with normal population. The raised risk seems related to the inflammatory burden of the disease as expressed by a high disease activity and elevated acute-phase reactants [67,68]. Like in RA, also in PsA anti-TNFs seem to reduce significantly the frequency of CVEs and risk factors for atherosclerosis [69]. However, no studies comparing the efficacy of different anti-TNFs in preventing cardiovascular complication in patients with PsA are available.

4.3. *Biologics and risk of infections.*

Concerns about the potential adverse events of biologics remain an important issue. It has been shown that inhibiting the cytokine effects by using the anti-TNF agents or ANK may impair the effectiveness of the host immune function in the defense against infectious organisms, thereby leading to an increased risk of infections, including the risk of opportunist infections [70,71]. Concomitantly, RA, SpA, and PsA are associated with double risk of infections as compared to matched controls [72,73]. This higher incidence may be related to the disease itself, extra-articular manifestations, comorbidities, use of immunosuppressive drugs, and corticosteroids [72,73].

There is limited evidence of a substantial increased overall risk of serious infections in patients exposed to anti-TNFs, particularly in patients receiving concomitant treatment with corticosteroids, or with comorbidity [30,74]. Probably, also older age, disease duration, disease activity, and type of biological treatment may have an impact on the augmented risk [30,74]. In this regard, despite some conflicting results, available meta-analyses seem to confirm a trend to a lower infection risk associated with ETN with respect to the other anti-TNFs [54]. An increased risk of infection has been observed in ANK- and TCZ-exposed patients [70,75], while available data show the lowest infection risk profile for ABA and UTK [76]. An increased risk of perforation in patients with a

history of infected intestinal diverticulosis receiving TCZ has been observed, hence avoiding this drug in such patients would be preferable [77].

Data from national registries and post-marketing surveillance showed an increased risk of TB in patients receiving IFX, ADA, and ETN, with a 3–4 times higher risk associated with IFX and ADA than with ETN. However nonconformities from recommended TB prevention procedures were observed in up to 80% of patients in whom active TB was diagnosed and most registries did not include data on host-related risk factors for TB, thus making difficult to understand the reasons behind TB development [57]. No increased risk of TB reactivation is associated with non-anti-TNF targeted biologics, including TCZ, ABA, UTK, and RTX [57].

Hepatitis B virus (HBV) reactivation has been described in patients exposed to anti-TNFs [56]. Although the role of TNF-α in chronic viral hepatitis is limited, there is evidence that TNF-α synergizes with interferons in suppressing viral replication, and is essential in clearing HBV [78]. Hence, all patients should be screened for HBV before anti-TNF starting, and if active HBV replication is detected, antiviral treatment should be administered [56]. As regards, Hepatitis C virus (HCV) reactivation the use of anti-TNFs is safe, whereas the therapy with RTX significantly increases HCV viral load suggesting that RTX treatment should be performed in combination with antiviral therapy for HCV [79].

The potential association between anti-TNF therapy and herpes zoster (VZV) is not clear. A German study, including 5,040 patients with RA, reported that exposure to IFX and ADA was associated with an 82% significant increased risk after adjustment for age, disease severity and glucocorticoid use [80]. However, a recent study, including 33,324 patients with RA, IBD, PsA, AS, and psoriasis receiving anti-TNFs did not confirm a higher risk of VZV infection [81]. Hence, despite these conflicting results, clinicians should be aware of the potential increased risk of VZV infection, particularly in the light of the high prevalence of VZV seropositive patients.

Cytomegalovirus (CMV) is another member of the Herpes virus family and is a widespread infection in adults and children [82]. The primary infection in immune-competent patients is nearly

always asymptomatic, but afterwards the infection often becomes latent. Data on the possible anti-TNF-induced latent CMV infection reactivation are conflicting [83], therefore handling of CMV infection in patients requiring biologics remains a challenge.

Pneumocystis jirovecii (PJP) is an opportunistic fungal respiratory pathogen responsible for pneumonia. An increased risk of PJP has been suggested to be associated with anti-TNFs, especially in Japan [84]. However, most studies worldwide have reported low incidences of PJP of less than one case per 1000 person-years follow-up [83].Therefore, a systematic chemoprophylaxis for PJP is not recommended.

Finally, all killed vaccinations, including Influenza (annual), Pneumococcal, Hepatitis B, VZV, HPV (only in women) are recommended prior to the initiation of anti-TNFs [1].

4.4. *Biologics as monotherapy in RA*.

Biologics are usually combined with traditional DMARDs (tDMARDs), primarily MTX, but in real life, approximately 30% of RA patients receive biologic monotherapy [86-88].

In recent review of 17 RCTs evaluating the efficacy on patient reported outcomes of ADA, CTP, ETN, GOL, IFX, or TCZ in monotherapy compared to combined therapy with MTX in inadequate responders to tDMARDs, TCZ monotherapy was associated with a greater improvements in pain and self-reported disease activity and functional ability as compared with anti-TNFs [89].

However, some evidence of efficacy of ETN, and ADA employed as monotherapy is available. ETN monotherapy resulted significantly more effective than MTX in improving signs and symptoms, and in inhibiting the radiographic progression in patients with early RA [90,91]. In ERA and TEMPO trials ETN monotherapy resulted not superior to MTX in terms of clinical outcomes, but a significant difference in radiographic progression inhibition was observed in ETN cohort with respect to MTX group [92,93].

Similarly, in the PREMIER study [94], ADA monotherapy resulted significantly more effective in inhibiting the radiographic disease progression compared to MTX monotherapy.

Both GOL and CTP monotherapy resulted effective in improving the signs and symptoms of active RA in patients failing at least one tDMARD or in MTX naïve subjects [95,96]. However, as observed for the other anti-TNF agents, GOL and CTP efficacy was higher in combination therapy with MTX [97].

A clear evidence of superior efficacy of TCZ monotherapy resulted from several studies. The AMBITION trial demonstrated a significantly higher ACR20/50/70 response and a larger proportion DAS28 remission in the TCZ monotherapy treatment arm as compared with MTX group [98].

The ADACTA study was conducted to compare TCZ monotherapy at the dose of 8 mg/kg/iv/every 4 weeks, to ADA monotherapy 40 mg/sc/ every other week in RA patients intolerant to MTX [99]. At 24-week visit, TCZ monotherapy resulted significantly more effective in DAS28 score reduction compared to ADA monotherapy.

Confirming previous results, in the ACT-RAY trial TCZ monotherapy resulted significantly superior to MTX in reducing the signs and symptoms of RA with a sustained effect at week 52 [100].

Finally, a recent network meta-analysis of twenty-eight RCTs with DMARD-naïve and DMARD-inadequate respnders RA patients, confirmed that TCZ monotherapy was associated with a higher ACR response compared to ABA, ANK, ADA, CTP,ETN, GOL, IFX monotherapy [101].

4.5. *Response predictor biomarkers in RA, AS, and PsA.*

The role of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) as predictors of response to different biologics has been extensively evaluated in patients with RA. Although some conflicting results, most studies demonstrated an inverse relationship between high baseline titers of RF and response to anti-TNFs [102,103], whereas no consensus resulted on the usefulness of basal ACPA levels as a predictor of clinical response to the same biologic class [104]. However, independently on the baseline levels, the response to anti-TNFs has been associated to a decrease of

RF [105,106], while a less striking evidence is available on the reduction of ACPA serum levels [107].

RF positivity resulted a good response predictor in RA patients receiving RTX, and TCZ, but not ABA [108,109]. Observational studies of patients with RA treated with RTX demonstrated that RF positive patients achieved a significantly greater reduction of DAS28 compared to seronegative patients [110,111], while no significant relationship with ACPA titers was found [110]. Of note, data from a large French cohort of 773 patients with RA included in the ORA registry showed that ACPA positivity, independently on baseline disease activity, was associated with a better response to ABA [112].

Beyond the predictive role of RF and ACPA serum levels, other biomarkers, including serum calprotectin, immunoglobulin free light chains (FLC), matrix metalloproteinase-3 (MMP-3), serum cartilage oligomeric matrix protein (COMP) are under investigation. Serum calprotectin has been recently proposed as a promising myeloid serum marker of inflammation and response to therapies [113,114].

FLC, circulating lymphoid biomarkers of B cell activity in RA, have been recently reported as predictors of response to RTX and ABA [115,116].

Studies on the relationship between MMP-3 and COMP serum levels and RA disease activity, and the response to anti-TNFs and TCZ as well, are ongoing with promising results [117-119].

Several soluble bone and cartilage turnover biomarkers, including MMP-3, Dickkopf (DKK)-1, macrophage colony-stimulating factor (M-CSF), cross-linked telopeptide of collagen-1, and tumor necrosis factor-related apoptosis-inducing ligand, are under investigation to evaluate the possible association with PsA diagnosis and disease activity [120]. However, no conclusive data are available. No response predictor biomarker has been identified for SpA.

4.6. *The role of dismetabolic and cardiovascular comorbidity in the selection of biologics.*

RA increases the risk of cardiovascular (CV) mortality by up to 50% compared with the general population, and CV disease (CVD) is the leading cause of death in RA patients [121,122]. Although

less striking than in RA, an increased CVD risk has been also recorded in patients with psoriasis (Pso), PsA, and AS [67,68, 123-124]. Beyond the increased prevalence of traditional CV risk factors, such as smoking, diabetes mellitus or lower high-density lipoprotein cholesterol (HDL) levels and hypertension, observed in RA patients [125,126], the systemic inflammatory burden associated with the disease plays a pivotal role in accelerated atherosclerosis and increased CV morbidity and mortality [127]. Hence, early treatment with achievement of low disease activity or remission ensures a better structural and functional outcomes, and reduces CV risk [128].

Confirming previous reports [129-131], in a recent meta-analysis anti-TNFs were significantly associated with a reduction in the risk of all cardiovascular events (CVEs) both in RA and PsA [69], whereas conflicting results have been found in AS patients [132,133].

In RA, inflammation is associated with a paradoxical inversion of the usual relationship between CV risk and lipid levels, with lower total cholesterol (TCh) levels as well as lower levels of HDL and low-density lipoprotein cholesterol (LDL) [134]. Available meta-analyses indicate that anti-TNFs are generally associated with significant increases in HDL, TCh and triglycerides, with no significant changes in atherogenic index [135,136]. Hence, the reported cardio-protective effects of anti-TNFs in RA do not seem to be explained by the quantitative lipid changes.

Evidence has been accumulating on the important role of inflammation in the pathogenesis of type 2 diabetes mellitus [137]. Several soluble markers of systemic inflammation are increased in type 2 diabetes and elevated serum concentrations of key inflammatory cytokines such as IL-1, TNF, and IL-6 are associated with insulin resistance [138].

The results of longitudinal studies have shown that anti-TNFs improve insulin resistance and may favorably alter glucose metabolism with reduction of the risk for diabetes in RA patients [139-140]. However, a trial of ETN failed to improve insulin sensitivity in subjects with RA and metabolic syndrome despite lowering CRP [141]. Similarly, ADA, ETN, and IFX did not have any effect on glucose metabolism in patients with PsA, AS, and juvenile idiopathic arthritis [142]. By contrast, in a recent short-term, open-label study of 92 RA patients, anti-TNFs significantly improved both the

lipid profile and the insulin resistance [143].

Conflicting results on the impact of anti-TNFs on arterial blood pressure have been reported. However, a recent meta-analysis of randomized controlled trials demonstrated a significant increased risk of developing hypertension in RA patients [144].

Few data on the effects on non-anti-TNF targeted biologics on CV risk are available.

TCZ is associated with increased lipid levels, but with no appreciable changes of TCh:HDL ratio [145]. In an analysis of five phase III studies of TCZ, CVEs were numerically lower in the active treatment arms as compared with controls, with a stable overtime CVE rate [146]. Moreover, in a sub-analysis of the TOWARD study TCZ significantly improved the insulin resistance in RA patients [147].

IL-1 is implicated in atherogenesis and contributes to an impaired insulin secretion, decreased cell proliferation, and apoptosis of pancreatic ß cells. Consequently, promising results of efficacy on type 2 diabetes have been observed in patients treated with ANK [148]. In addition, a large multicenter trial on the efficacy of monoclonal anti-IL-1 beta canakinumab to prevent CVEs is ongoing [149].

Little is known regarding the impact of RTX, ABA, and UTK on lipid profiles, and CV risk in RA, and PsA [150,151].

4.7. Pregnancy and biological therapies.

Maternal immunoglobulins (IgGs) are actively transported across the placenta by selective binding to the neonatal Fc receptor; thus, IgGs are found in fetal serum as early as 13 weeks of gestation, with a continuous rise in the transfer of IgG to the fetus as the pregnancy advances [152].

Because IFX and ADA are both complete IgG1 antibodies, they are actively transported across the placenta and their transfer increases significantly in the third trimester with minimal active transfer in the first trimester during the crucial period of organogenesis [153].

ETN is a dimeric fusion protein linked to an IgG1 Fc portion. A low trans-placental passage has been shown in isolated cases; in addition, very low levels in breast milk, and no detected absorption by the child have also been reported [154,155].

CTP is the only PEGylated, humanised, antigen-binding fragment of an anti-TNF monoclonal antibody and it is not actively transported across the placenta during pregnancy; however, the Fab' fragment may passively cross the placenta in low levels during the first trimester.

Drug concentrations in the cord blood and in the infant at birth have been evaluated in 31 pregnancies exposed to IFX, ADA and CZP. At birth, the median levels of IFX, ADA, and CTP compared with that of mother were 160%, 153%, and 3.9%, respectively, and IFX and ADA could be detected in the infants for as long as 6 months [156].

A recent review of 58 studies including 1822 pregnancies in women receiving anti-TNFS for IBD or rheumatic conditions showed no adverse outcomes in terms of stillbirth, low birth weight, congenital malformations, or risk of infections in the offspring [157], while a slight increased rate of birth defects, a significantly lower birth weight, and a higher rate of preterm births was found in 495 pregnancies exposed to ADA, IFX, ETA, CZP, or GOL [158]. In addition, no increased teratogenic risk was observed in 83 anti-TNF-exposed pregnancies [159], and no effects on growth and psychomotor development was found in a small series of 25 children exposed to anti-TNFs prenatally [160].

RTX is a chimeric murine/human monoclonal IgG1 kappa immunoglobulin. The RTX global drug safety database reported an increased rate of spontaneous abortions and prematurity, mild and transient neutropenia and B cell depletion in 12% of the neonates, but no neonatal deaths or congenital malformations [161-163].

No published studies of ABA, ANK and TCZ are available so far.

4.8. Patient preference and adherence and biologic choice.

Data from the literature show that the adherence to biologic therapies in patients with RA ranges between 50% to 70%, with a higher adherence in patients treated with intravenous administration route compared to those receiving subcutaneous therapies [164-166].

As reported in a recent questionnaire-based study on 182 women and 68 men with RA treated with anti-TNF [167], the main reasons for therapy discontinuation were related to lack of effectiveness in 40%, concerns about safety and tolerability in 30%, injection discomfort or reactions in 18%, respectively. Additional factors associating with a lower adherence to biologic therapies were the female gender, the increasing therapy duration, while the increasing disease duration was related to a better adherence [168].

In a recent British, large multicenter, prospective, observational cohort study on 392 RA patients [169], 27% of the patients resulted ever non-adherent during a 6-month period, and a significantly lower clinical DAS28 response was recorded in this group.

Several variables are known to influence the drug adherence, such as therapy- and patient-related factors, and the good link between the patient and the medical team [170]. Beyond the great importance of therapy efficacy and tolerability, the route of administration consistently influences the adherence. In general, patients prefer self-administered subcutaneous biologics with the longest injection intervals [171-173]. However, this preference is less stringent in aged patients, who are less confident with self-injection and prefer a tight relationship with the medical team [171].

Other patient characteristics influencing the adherence are of importance for the decision, including the level of education, the socio-economic status, the ability to move from home to hospital, and the body mass index. Finally, intravenous administration route, by allowing the dose titration, is preferable in patients with a body mass index greater than 30 Kg/m^2 [174,175].

4.9. Cost-Effectiveness of biological therapies.

Several systematic reviews suggested that biologics might be cost-effective at the willingness to pay (WTP) threshold of 50,000–100,000 $/QALY (quality adjusted life years) among tDMARD non-responsive patients, but not in tDMARD naïve [176–178].

Four studies evaluated the economic impact of biologics compared to tDMARDs [179-181]. IFX was associated with the highest ICERs ranging from 422,000 to 1273,000 €/QALY, while ICERs for ETN and ADA as a monotherapy were below 100,000 €/QALY. ICER values for ETN and ADA were substantially higher if employed in combination therapy with MTX.

Three more studies examined the cost-effectiveness of different treatment strategies for early RA including anti-TNFs in all treatment options, with only its time of usage in a treatment sequence being altered [183-185]. In two of these reports a late introduction of anti-TNFs resulted to be a dominant strategy compared to early initiation of the treatment [184,185].

Studies calculating the cost-effectiveness of biologics in RA patients non-responders to tDMARDs have shown that ICERs for IFX, ADA and ETN were 12,000–282,000; 44,000–274,000 and 40,000–708,000, respectively. ABA and TCZ were associated with narrower ICER ranges (42,000 to 47,000 and 19,000 to 21,000, respectively)[186-191]. ICERs below 35,000 €/QALY were found in three studies [190-192], and below 50,000 €/QALY in seven studies [187,192-197]. Conflicting results were recorded in studies comparing the cost-effectiveness of different biologics used in patients with an inadequate response to tDMARDs [187, 198-203]. Two studies found ETN to be dominant over IFX and ADA [200,201], while three reported an ICER ranging from 23,000 to 109,000 €/QALY for ETN when only direct costs were included [187,198,199]. One more report reported ETN to be dominant over IFX and ADA [204]. while in another ETN was dominant over IFX but not over ADA [205].

Compared to RA, fewer studies have been published on the cost-effectiveness of biologic therapies in AS and PsA. However, ETN resulted more cost-effective in both conditions compared to other anti-TNFs [206-208].

Finally, the recent introduction of bio-IFX can lead to substantial savings in health care budgets [209].

5.0. *Evidence-based algorithms for tailored biologic therapy in patients with RA, AS, and PsA*.

As described in previous paragraphs, several choice driving variables should be taken in account to optimize the biological therapy in patients with RA, AS, and PsA. Some of these variables, including the patients' preference for self-administered subcutaneous route with the longest administration intervals, the indication for anti-TNF monotherapy in potential childbearing women, and its interruption at positivity of pregnancy test, are valid for all the three rheumatic conditions. In addition, the intravenous route, allowing the weight-related dose adjustment, is advisable in obese patients with RA, AS, and PsA. Further, evidence of a better cost-effectiveness profile for ETN in RA and to a lesser extent in AS and PsA is available.

5.1.Tailored biological therapy in RA.

As resumed in figure 1, no evidence is available for the most appropriate biologic choice in RA vasculitis or lung disease. Any biologic approved for first-line RA therapy may be employed in absence of choice driving factors. Otherwise, ABA in patient at high risk of infection, and ABA or TCZ in LTBI positive should be preferred, while ETN may be secondarily chosen. When monotherapy is required, TCZ should be the first choice, and, if TCZ is contraindicated (i.e. history of intestinal diverticulosis) ABA or any anti-TNF may be started. Taking in account that RTX is approved only as second-line therapy, high RF and ACPA titers should drive the choice toward TCZ or ABA, while in patients at high CVD risk anti-TNF choice, with preference for ETN, seems appropriate. Practical indication for biologic choice in the case of anti-TNF primary or secondary failure are also summarized in figure 1.

5.2.*Tailored biological therapy in SpA.*

To date, the first line biologic choice in patients with SpA is limited to anti-TNF agents. Figure 2 show the evidence-based decisional tree. If no additional choice driving variables are present, any anti-TNF, with a slight preference for IFX and bio-IFX, may be employed in patients with AS, while in non-rx-AxSpA only ADA, CTP, and ETN have been approved. Presence of anterior uveitis or IBD drives the choice to MoAb anti-TNF, while ETN would be preferred in presence of infection

and TB risk or in patients with metabolic syndrome or elevated CVD risk.

5.3.*Tailored biological therapy in PsA.*

The decisional tree for first line biologic choice in PsA is reported in figure 3. Taking in account that in presence of pregnancy risk anti-TNF should be chosen, patients with no additional choice driving variables may be treated with any approved biologic, while UTK, and to a lesser extent ETN, may represent the best choice in patients at high risk of infection and TB. As indicated, since UTK is more effective on psoriasis than on arthritis, skin or articular disease severity drives the choice to anti-TNF of UTK, while MoAb-anti-TNFs should be employed in patients with anterior uveitis. Enthesitis and dactylitis are important features that drive the choice to IFX or UTK, whereas ETN as first line or MoAb-anti-TNFs should be preferred if metabolic syndrome or high CVD risk complicate PsA. It should be noted that in next future the therapeutic scenario of biologic choice for PsA therapy will enlarge with the up-coming approval of anti-IL-17 targeted agents including secukinumab and ixekizumab (210,211).

6.0 *Conclusion.*

Several evidence-based, choice driving variables have been identified to optimize the first line biologic therapy in patients with RA, SpA, and PsA. Overall results coming from direct and indirect comparative studies in RA show that no driving biologic choice indicators can be expressed in terms of efficacy on clinical response, damage progression, and functional status. TCZ represents the optimal choice if monotherapy is needed in RA, while RF and ACPA high titers drive the choice toward TCZ and ABA. ABA in RA, ETN in SpA, and UTK in PsA should be preferred in patients with an elevated infection and TB risk. In women at pregnancy risk anti-TNF agents should be employed. MoAb anti-TNFs cover all clinical manifestations of SpA and PsA, but the presence of enthesitis and dactylitis drives the choice to IFX or UTK. Anti-TNFs, with preference for ETN, offer better results in patients at high CVD risk. Finally, evidence of cost-effectiveness of ETN is available, but bio-IFX can lead to superior cost savings. Based on these data, the ITABIO task force

prompted the decisional trees that may offer useful indication in clinical practice.

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Table1. Evidence-based ITABIO statements for tailored first-line biologic therapy in RA, SpA, and PsA

Clinical variable	Statements		
	RA	SpA	PsA
Efficacy	1.-Except for the lowest efficacy of ANK, no driving biologic choice indicators can be expressed. 2.Baseline RA severity does not constitute a driver for choosing the first-line biologic. 3.Though debated, anti-TNF registries indicate that ETN has the longest drug survival. No sufficient data are available for other non-anti-TNF targeted biologics.	1.Slight preference for IFX or bio-IFX. 2.Presence of EAMs suggests MoAb anti-TNFs.	1.Presence of AAU suggests MoAb anti-TNFs. 2.Dactylitis may drive the choice toward IFX, CTP, and UTK. 3.UTK may be indicated in patients with severe psoriasis and mild arthritis.
Infection risk*	1.Among anti-TNFs, ETN is associated with the lowest risk. 2.ABA does not seem to increase the infection risk. 3.In LTBI positive, TCZ, ABA, and to a lesser extent ETN, are advisable.	1.ETN is associated with the lowest risk. 2. In LTBI positive, ETN is advisable.	1.UTK does not seem to increase the infection risk. 2.In LTBI positive, UTK is advisable, and alternatively ETN.
Monotherapy	1.Lower radiographic progression in patients treated with anti-TNF compared with MTX. 2. No safety differences between combined therapy and monotherapy 3.Evidence of superiority of TCZ compared to MTX.	Not applicable	Not applicable
Response predictor biomarkers	1.Baseline high levels of RF are response predictors to RTX and to a lesser extent to TCZ. This evidence is less striking for anti-TNFs. 2.Baseline high levels of ACPA may predict the response to ABA. 3.Serum Calprotectin and FLC seem a promising markers.	1.No response predictors have been identified.	1.No conclusive data on the role of several soluble bone and cartilage biomarkers are available.
Cardiovascular risk	1.Evidence of reduction of CV risk for anti-TNFs, and to a lesser extent for TCZ. 2.Favorable impact of anti-TNFs, TCZ, and ANK on impaired glucose metabolism. 3.Paucity of data on impact of RTX, ABA, ANK.	1.Weak evidence of reduction of CV risk for anti-TNFs.	1.Anti-TNFs,with preference for ETN, should be preferred. 2.No data on UTK.
Pregnancy	1.Anti-TNFs discontinuation at the time of recognition of pregnancy is advisable. 2. If disease flare during pregnancy, the decision to	1. Due to the lower age of disease onset the pregnancy risk is higher.	1.No available data for UTK

	continue anti-TNFs α should be based on a case-by-case weighting benefits and risks in a multidisciplinary setting. 3.Discontinuation of anti-TNFs is recommended no later than 30 weeks of pregnancy. 4.Before pregnancy, a wash-out period of at least 5 terminal half-lives for TCZ and ABA can be reasonable . 5.An increased rate of spontaneous abortions in RTX exposed results from hematology series.		
Patient preference**	1.Most patients prefer home self-administered biologics at the longest administration intervals. 2.Intravenous administration ensures the better adherence. 3.Intravenous route is advisable in obese patients. 4.A careful evaluation of patient working and socio-economic status, education, intelligence level, distance from the rheumatologic center is required.	See footnote*.	See footnote*.
Cost-effectiveness	1.ETN results cost saving compared to other anti TNFs. 4.Bio-IFX can lead to substantial savings in health care budgets.	Weak evidence for ETN as cost-effective.	Weak evidence for ETN as cost-effective.

Footnotes. *Statements 1,2 and 3 are valid also for SpA and PsA; ** All 4 statements are valid also for SpA and PsA.

Abbreviations. RA: rheumatoid arthritis; SpA: spondyloarthritis; PsA: psoriatic arthritis; ANK: anti-TNFs: anti-tumor necrosis factor agents; anakinra;ETN: etanercept; IFX: infliximab; bio-IFX: biosimilar infliximab; TCZ: tocilizumab; ABA: abatacept; RTX: rituximab; UTK: ustekinumab; MoAb anti-TNFs: monoclonal antibody anti-TNFs; CV: cardiovascular; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; FLC: immunoglobulin free light chains.

Figure 1. ITABIO recommendations for first-line biologic choice in RA

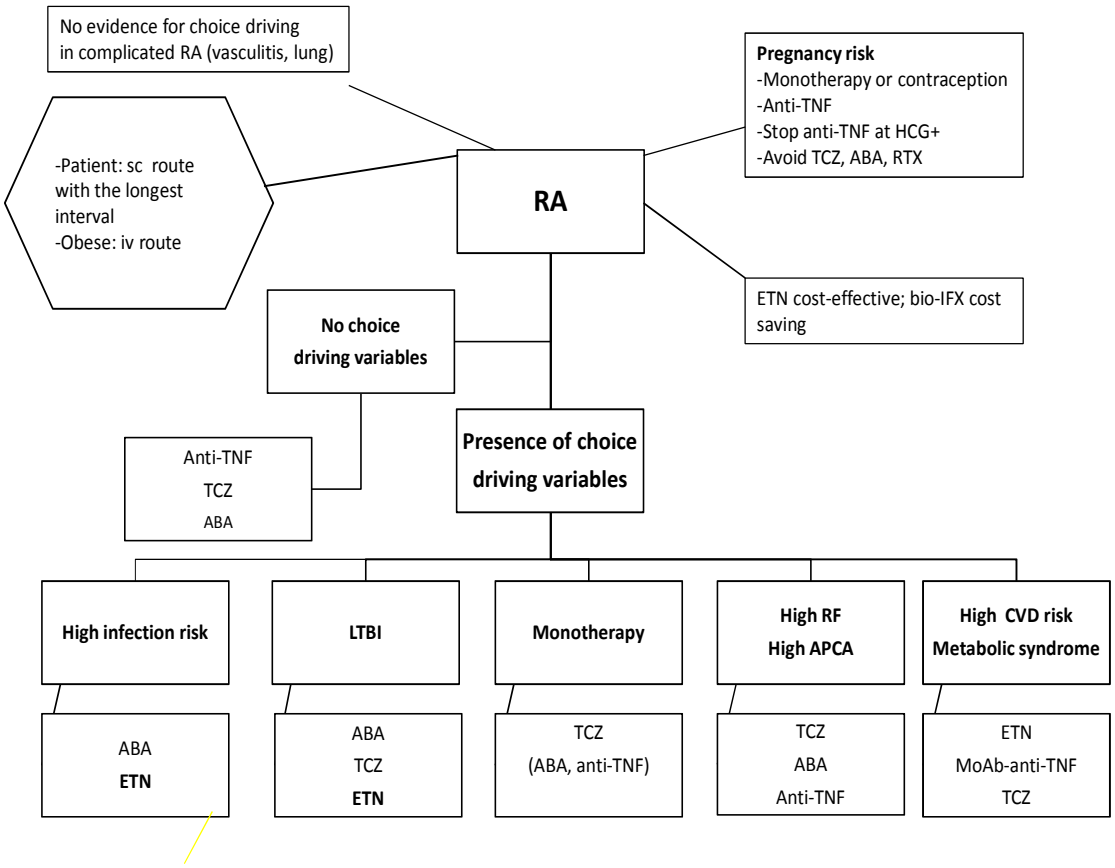
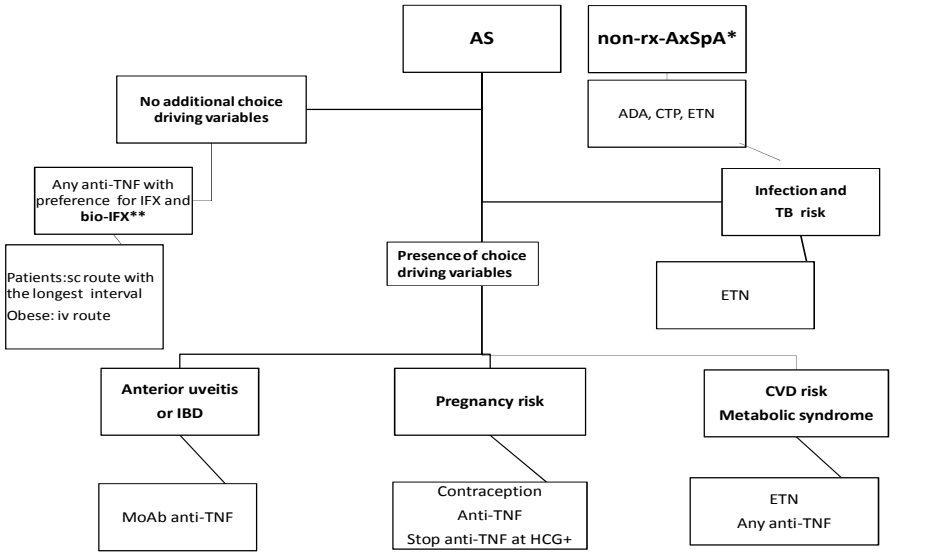


Figure 2. ITABIO recommendations for first biologic choice in AS and non-Rx axial SpA.



***Only ADA, CTP and ETN have been approved for non-rx-AxSpA in Europe.**
**** See text.**

Figure 3. ITABIO recommendations for first biologic choice in patients with PsA