ORIGINAL PAPER

The data project: a shared approach between stakeholders of the healthcare system in definition of a therapeutic algorithm for inflammatory arthritis

I. Pantano[1], D. Mauro[1], D. Simone[1], L. Costa[2], D. Capocotta[3], M. Raimondo[4], D. Birra[5], G. Cuomo[1], T. D'Errico[6], M. Ferrucci[7], F. Comentale[8], G. Italiano[9], P. Moscato[5], N. Pappone[10], R. Russo[11], S. Scarpato[12], R. Tirri[1], P. Buono[13], A. Postiglione[14], R. Guida[15], R. Scarpa[2], U. Trama[15], E. Tirri[3], F. Ciccia[1]

[1]Rheumatology Unit, Department of Precision Medicine, University della Campania 'L. Vanvitelli', Naples, Italy; [2]Rheumatology Unit, University Federico II of Naples, Naples, Italy; [3]Rheumatology Unit, San Giovanni Bosco Hospital, Local Health Company, ASL NA1, Naples, Italy; [4]Internal Medicine, S. Giuseppe Moscato Hospital, Avellino, Italy; [5]Rheumatology Service, San Giovanni di Dio e Ruggi Hospital, Salerno, Italy; [6]Rheumatologist, Local Health Company, ASL NA1, Naples, Italy; [7]Rheumatology Unit, Rummo Hospital, Benevento, Italy; [8]Rheumatologist, Local Health Company, ASL NA3 Sud, Naples, Italy; [9]Internal Medicine, Sant'Anna e San Sebastiano Hospital, Caserta, Italy; [10]Rheumatological Rehabilitation Unit, Maugeri Foundation, Telese, Italy; [11]Rheumatology Unit, Antonio Cardarelli Hospital of Naples, Naples, Italy; [12]Rheumatology Unit, Scarlato Hospital, Scafati (SA), Italy; [13]STAFF 91 Unit, Regione Campania, Naples, Italy; [14]General Direction for Health Protection and Coordination of the Regional Health System, Regione Campania, Naples, Italy; [15]Drug Policy and Devices Unit, Regione Campania Health Department, Naples, Italy

SUMMARY

Rheumatic musculoskeletal diseases or RMD [rheumatoid arthritis (RA) and spondyloarthritis (SpA)] are systemic inflammatory diseases for which there are no biomarkers capable of predicting treatments with a higher likelihood of response in naive patients. In addition, the expiration of the anti-TNF blocking drugs' patents has resulted in the availability of anti-TNF biosimilar drugs with the same efficacy and safety than originators but at significantly reduced prices. To guarantee a personalized therapeutic approach to RMD treatment, a board of rheumatologists and stakeholders from the Campania region, Italy, developed a clinically applicable arthritis therapeutic algorithm to guide rheumatologists (DATA project).

The general methodology relied on a Delphi technique forecast to produce a set of statements that summarized the experts' consensus. Selected clinical scenarios were discussed in light of the available evidence, and there were two rounds of voting on the therapeutic approaches.

Separate discussions were held regarding rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The decision-making factors for each disease were clinical presentation, demographics, and comorbidities.

In this paper, we describe a virtuous process between rheumatologists and healthcare system stakeholders that resulted in the development of a shared therapeutic algorithm for RMD patients naive to bDMARDs.

Key words: *Precision medicine, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, therapeutic algorithm.*

Reumatismo, 2022; 74 (4): 151-159

INTRODUCTION

Musculoskeletal rheumatic diseases or RMD [rheumatoid arthritis (RA) and spondylarthritis (SpA)] are systemic inflammatory diseases which are characterized by a high level of morbility and mortality, as well as significantly high social costs (1, 2). The widespread use of biotechnological drugs in clinical practice has significantly changed the natural history of RMD patients, allowing for excellent control of inflammatory manifestations and halting the progression of structural damage. Several classes of biotechnological medications are currently available for the treatment of

Corresponding author:
Francesco Ciccia
Rheumatology Unit,
Department of Precision Medicine,
University della Campania 'L. Vanvitelli',
Naples, Italy
E-mail: francesco.ciccia@unicampania.it

RMD. However, the absence of a predictor of response at the level of a single patient makes therapeutic decision-making difficult. Patients' characteristics may influence the selection of one mechanism of action over another, given the current state of medical knowledge (3). The expiration of patents for anti-TNF blocking drugs makes several anti-TNF biosimilar drugs more affordable, thereby contributing to a higher possibility for the National Health System to sustain RMD therapies (4, 5). However, the fragmentation of the Italian National Health System into regional systems has resulted in a heterogeneity of rules in which economic evaluation is frequently the determining factor. In many Italian Regional Health Systems, this resulted in a significant restriction of patients' access to innovative treatments and of physicians' freedom of choice. In recent years, in the Italian Campania Region, a fruitful collaboration between the rheumatologist and the management health department has paved the way for a shared project called DATA (*d*efinition of *a*rthritis *t*herapeutic *a*lgorithm) to guide the selection of the first bDMARD in patients with inflammatory arthritis. Based on scientific evidence and fundamental pharmacoeconomic considerations, the board developed clinically applicable therapeutic algorithms. Rheumatologists in Campania currently use these algorithms, which became an integral part of a resolution of the Region's Health Department in November 2021, to provide patients with access to the most appropriate treatments.

METHODS

The methodology relied on a Delphi technique prediction to generate a set of statements summarizing the consensus of a Scientific Regional Committee (SRC) comprised of experts, fellows, and members of the local health office.

Specifically, the SRC consisted of twenty rheumatologists from Campania, prescribers of biotechnological drugs, the director of drug policy, and managers from the Campania Regional Council.

The SRC identified relevant clinical scenarios for the treatment of RMD that deserve a consensus based on the available scientific evidence regarding the use of biotechnological drugs in patients with chronic arthritis. RA and SpA, including psoriatic arthritis (PsA) and ankylosing spondylitis (AS), were evaluated as RMD. Selected topics were analyzed by the SRC through a comprehensive bibliographic review.

As requested for each topic, the search strategy integrated indexed and free-text terms, interventions, and outcomes of interest from the Medline, PubMed, Scopus, and Cochrane databases. Along with pre-defined 'Population,' 'Intervention,' 'Comparison,' and 'Outcomes,' the PICO strategy served as a rephrasing strategy across working groups, as required by each topic research question. Included studies were English-language, full-text manuscripts conducted on adult patients with RMD. To be included in the final analysis, studies were required to report data regarding population, intervention, comparison, and outcomes for each topic individually. Then, three remote meetings were held on a dedicated digital platform. During each meeting for each clinical scenario, online surveys were used to record the approach to each participant. After the first round of voting, a summary of the current evidence was presented, and the statements were reformulated following an interactive analysis of the level of evidence. Subsequently, a second Delphi voting round was conducted for each scenario, resulting in the formulation of final recommendations. Recommendations supported by ≥75% of votes were accepted as final statements, whereas all others were outright rejected. This project was completed in March 2021 in Campania and published as a resolution by the health department of Campania in November 2021.

RECOMMENDATIONS

Role of comorbidities in influencing the choice of first bDMARD or tsDMARD in RMD

Comorbidities may influence the selection of treatment for RMD patients. Prevalent are metabolic diseases such as obesity or

overweight, diabetes, and metabolic syndrome. Obese RMD patients treated with TNF-inhibitors have a lower probability of remission than normal-weight patients (6-10). The panel agreed that treatment with mechanisms other than anti-TNF should be considered for obese patients (Tables I-III). The use of anti-IL-6 and anakinra has also been shown to significantly reduce glycated Hb in patients with RA and uncontrolled diabetes mellitus; therefore, the panel voted for the possible use of anti-IL-6 or anakinra as the first choice in these patients (11). Patients with RMD are also more likely to develop cancer than the general population (12). Since anti-TNFs are not associated with an increase in cancer risk, the panel voted to use them as the first line of treatment for patients with associated cancer (13). Some case reports have suggested a link between the use of anti-TNF or abatacept and the development of non-melanoma and melanoma skin cancers. In these particular patients, the panel advised avoiding anti-TNF treatment (14, 15). Apremilast was recom-

Table I - Statements voted for rheumatoid arthritis treatment.

Statements		Agreement
1	In RA patients unresponsive to methotrexate therapy in the absence of unfavorable prognostic factors, ineffectiveness, contraindication, or reaction to another csDMARD, an anti-TNF should be added as the first therapeutic option.	97%
2	In RA patients unresponsive to methotrexate therapy, in the presence of erosions as a negative prognostic factor, the addition of an anti-TNF or JAK-I should be the first therapeutic option.	92%
3	In RA patients with contraindications or intolerance to all DMARDs (methotrexate, leflunomide, sulfasalazine) in the presence or absence of unfavorable prognostic factors, therapy with JAK-I or anti-IL-6 should be preferred.	100%
4	In a female RA patient of childbearing age and an imminent desire for pregnancy, certolizumab should represent the first therapeutic option.	100%
5	In RA patients with a body mass index greater than 30 kg/m^2 bDMARDs alternative to anti-TNFs should be preferred.	100%
6	In overlap Sjogren's syndrome with rheumatoid arthritis patient, abatacept and rituximab should be preferred.	100%
7	In a patient with systemic sclerosis in overlap with rheumatoid arthritis, therapy with rituximab should be preferred.	100%
8	In a patient with systemic lupus erythematosus in overlap with rheumatoid arthritis, rituximab therapy should be preferred.	100%
9	In RA patients with high thromboembolic risk, anti-TNF therapy should represent the first therapeutic choice.	91%
10	In a RA patient with secondary interstitial lung disease, abatacept should represent the first therapeutic option.	100%
11	In RA patients with a previous solid tumor, except melanoma, anti-TNF therapy should represent the first therapeutic choice.	91%
12	In RA patients with previous skin cancer, melanoma and non-melanoma skin cancer, it is preferable to use therapy with Jak-I and anti-IL-6.	92%
13	In RA patients with recent hematological malignancy, therapy with rituximab should be preferred.	100%
14	In RA patients with demyelinating disease, therapy with anti-TNF should be avoided.	100%
15	In RA patients at high risk of severe infection, therapy with etanercept and abatacept should be preferred.	100%
16	In RA patients at high risk of opportunistic infection, anti-TNF therapy is preferred.	100%
17	In RA patients at high risk of herpes zoster infection, anti-TNF therapy is preferred.	91%
18	In RA patients with uncontrolled diabetes mellitus*, therapy with anakinra and anti-IL6 should be preferred.	100%
19	In RA patients with class III and IV NYHA heart failure, it is preferable to start therapy with abatacept, anti IL6 or JAK-I.	100%

*Uncontrolled diabetes mellitus is defined as glycated Hb>7.

mended as the sole treatment for PsA patients with concurrent cancer (16-18). In RA patients with a history of hematological malignancy, rituximab, which is also indicated in hematological diseases, was recommended (19).

Due to disease activity and immunosuppressive treatment, RMD patients are at an increased risk of infection (20, 21). Patients with a history of at least two infections requiring hospitalization or intravenous antibiotic treatment were deemed to be at high risk for infection by the panel. Registries and meta-analyses revealed that the prevalence of severe infection is greater in RMD patients treated with rituximab and anti-TNFs (22). However, the high prevalence of severe infections during infliximab therapy weighed heavily on the statistical analysis of each anti-TNF. Similar odds ratios are associated with the use of etanercept and severe infections. The panel therefore voted to use abatacept or etanercept in patients with a high risk of infection (23). Ustekinumab should be prescribed to PsA patients with a high risk of infection (24-

Table II - Statements voted for psoriatic arthritis treatment.

Statements		Agreement
1	An anti-TNF should be the first therapeutic choice in patients with psoriatic arthritis with an oligoarticular pattern unresponsive to cDMARDs.	100%
2	In a patient with psoriatic arthritis with predominantly axial involvement, an anti-TNF or anti-IL-17 drug should be the first therapeutic choice.	100%
3	In a patient with psoriatic arthritis with a prevalence of enthesitis or dactylitis, an anti-TNF drug should be the first therapeutic choice.	100%
4	In a patient with psoriatic arthritis with prevalent skin involvement (PASI>10, or psoriasis of the scalp, palms-plantar, inverse, genital), an anti-IL-12/23 or anti-IL-17 drug should be the first therapeutic choice.	100%
5	In a patient with psoriatic arthritis with prevalent nail involvement (onychopathy), an anti-IL-17 drug should be the first therapeutic choice.	100%
6	In a patient with psoriatic arthritis in association with inflammatory bowel disease, an anti-TNF drug (monoclonal antibody) should be the first therapeutic choice.	100%
7	In a patient with psoriatic arthritis and recurrent uveitis, an anti-TNF drug (monoclonal antibody) should be the first therapeutic choice.	100%
8	In a female patient of childbearing age with psoriatic arthritis with an imminent desire for pregnancy, certolizumab is the therapeutic choice.	100%
9	In a patient with psoriatic arthritis with BMI>30, an anti-IL-17 drug should be the first therapeutic choice.	100%
10	An anti-TNF drug should be the first therapeutic choice in patients with psoriatic arthritis and metabolic syndrome.	93%
11	An anti-TNF drug should be the first therapeutic choice in patients with psoriatic arthritis and uncontrolled diabetes mellitus*.	100%
12	In a patient with psoriatic arthritis and heart failure, NYHA class III-IV anti-TNF drugs should be avoided.	100%
13	In a patient with psoriatic arthritis and demyelinating disease, TNF drugs should be avoided.	100%
14	In a patient with psoriatic arthritis with a recent history of cancer (<5 years) currently, only in oncological follow-up, apremilast is the first therapeutic choice.	100%
15	In a patient with psoriatic arthritis at high risk of severe infection, an anti-IL-12/23 drug should be the first therapeutic choice.	93%
16	An anti-TNF drug should be the first therapeutic choice in patients with psoriatic arthritis at high risk of opportunistic infection or Herpes Zoster.	100%

*Uncontrolled diabetes mellitus is defined as glycated Hb>7.

Table III - Statements voted for ankylosing spondylitis treatment.

Statements		Agreement
1	In a patient with non-radiographic axial-SpA, an anti-TNF should be the first therapeutic choice.	92%
2	In a patient with ankylosing spondylitis unresponsive to NSAIDs, an anti-TNF should be the first therapeutic choice.	100%
3	In a patient with ankylosing spondylitis, in the presence of unfavorable prognostic factors of progression (cigarette smoking, high disease activity, presence of structural damage at baseline), it is possible to use, based on scientific evidence and expert judgment, as first therapeutic choice an anti-TNF or anti-IL-17.	100%
4	An anti-TNF bDMARD (adalimumab/infliximab) should be the first therapeutic choice in patients with ankylosing spondylitis and concomitant inflammatory bowel disease.	100%
5	An anti-TNF bDMARD (monoclonal antibody) should be the first therapeutic choice in patients with ankylosing spondylitis and recurrent uveitis.	100%
6	In a patient with ankylosing spondylitis with a BMI >30, an anti-IL-17 drug should be the first therapeutic choice.	100%
7	In a patient with ankylosing spondylitis and metabolic syndrome, an anti-TNF should be the first therapeutic choice.	100%
8	In a patient with ankylosing spondylitis and uncontrolled diabetes mellitus*, an anti-TNF should be the first therapeutic choice.	100%
9	In a patient with ankylosing spondylitis and NYHA class III-IV heart failure, an anti-IL-17 drug should be the first therapeutic choice.	100%
10	In a female patient of childbearing age with ankylosing spondylitis with an imminent desire for pregnancy, certolizumab should be the first therapeutic choice.	93%
11	In a patient with ankylosing spondylitis and concomitant demyelinating disease, an anti-IL-17 drug should be the first therapeutic choice.	100%
12	An anti-TNF should be the first therapeutic choice in a patient with ankylosing spondylitis with a recent history of solid or hematological malignancy (<5 years) currently only in oncological follow-up.	100%
13	In a patient with ankylosing spondylitis with a recent history of skin cancer (melanoma or non-melanoma skin cancer), an anti-IL-17 drug should be preferred.	100%
14	In a patient with ankylosing spondylitis at high risk of severe infection, anti-TNFs should be the first therapeutic choice.	100%

*Uncontrolled diabetes mellitus is defined as glycated Hb>7.

26). Since anti-IL-17 use increases the risk of candidiasis and anti-IL-12/23 data are limited, the panel agreed that anti-TNF should be used in patients at risk of opportunistic infection (27).

In the presence of overlap diseases between RA and Sjogren's syndrome (SS), systemic sclerosis (SSc), and systemic lupus erythematosus (SLE), rituximab and abatacept were regarded as the drugs to be used due to their efficacy in connective tissue diseases (28, 29).

Compared to anti-TNF, patients with rheumatoid arthritis who are treated with JAK-inhibitors (JAK-I) have a higher risk of thromboembolic complications. Therefore, it is prudent to screen patients for thromboembolic risk factors, avoiding JAK-I in patients at high risk (30).

Up to 10% of patients with RA also develop pulmonary interstitial disease. Abatacept was chosen as the drug of choice because it can improve symptoms and lung function test parameters in RA patients with secondary interstitial lung disease (31-33). Anti-TNF monoclonal antibodies (infliximab and adalimumab) are also recommended for the treatment of inflammatory bowel disease (IBD) and uveitis in patients with SpA (34, 35). For this reason, the panel voted for TNF-targeting monoclonal antibodies as the first-line therapy for SpA patients with IBD or uveitis. Anti-TNF therapy is associated with the devel-

opment of demyelinating diseases of the peripheral and central nervous systems (36); therefore, patients with a history of demyelinating diseases should not receive anti-TNF therapy.
Finally, the CRIB and CRADLE trials demonstrated that certolizumab does not cross the placental barrier and is transferred into breast milk in only trace amounts (37, 38): therefore, it was designated as the drug to be administered to young women who are pregnant or who intend to become pregnant within the next few months (not women of fertile age in general).

Rheumatoid arthritis

The European Society of Rheumatology (EULAR) has identified negative prognostic factors (Table IV) for RA that may prompt clinicians to adopt a more aggressive therapeutic approach (39). All the different mechanisms of action are placed at the same level by the EULAR guidelines, effectively leaving prescriptive freedom. Due to the lack of head-to-head studies comparing different mechanisms of action, the panel of experts agreed to implement an anti-TNF as the first line of therapy. However, pivotal studies of JAK-I have revealed superiority data over anti-TNFs, effectively calling their use as the initial drug (40). Due to the lack of conclusive data on this topic in patients who already had erosions at the time of observation, the panel allowed for the possibility of choosing between anti-TNF and JAK-I. If a monotherapy is required, the panel voted to use an anti-IL-6 or JAK-I agent (39) (Table I).

Table IV - Negative prognostic factors in rheumatoid arthritis according to EULAR recommendations.

Negative prognostic factors in rheumatoid arthritis
Persistently moderate or high disease activity despite conventional synthetic DMARD (csDMARD) therapy according to composite measures including joint counts.
High acute phase reactant levels.
High swollen joint count.
Presence of RF and/or ACPA, especially at high levels.
Presence of early erosions.
Failure of two or more csDMARDs.

Psoriatic arthritis

PsA is a heterogeneous disease characterized by multiple domain involvement: peripheral joint, axial, enthesitis, dactylitis, and skin. Consequently, the clinical presentation and extra-articular manifestations influence the selection of treatment. According to EULAR recommendations, the first therapeutic option for oligoarticular disease is anti-TNF (35). According to the Maximize study, rheumatologists can choose between anti-TNF and anti-IL-17 in patients with PsA and axial involvement (41). The selection of anti-TNF in patients with enthesitis or dactylitis, as most important manifestation, is based on a 2018 meta-analysis that found no significant differences in efficacy between anti-TNF and anti-ILs (42). Although in the ECLIPSA study, ustekinumab was superior to anti-TNF in reducing enthesitis as measured by the SPARCC score, the panel deemed this evidence to be of low quality (43). The panel voted for the use of anti-IL12/23 or anti-IL17 in cases of severe skin involvement, defined as an extension of psoriasis greater than 10 percent of the body surface or as localization of psoriasis in particular areas such as hands, face, scalp, genital region, or as a patient's perception of high disability due to psoriasis (44, 45). Although psoriatic onychopathy is difficult to treat, IL-17 blockade has demonstrated greater clinical efficacy in the treatment of psoriatic onychopathy (46, 47) (Table II).

Ankylosing spondylitis

According to EULAR recommendations, anti-TNF is the first-line therapy for patients with non-radiographic axial SpA or AS who do not respond to NSAIDs (48). Male sex, cigarette smoking, high disease activity, elevated CRP levels, and baseline structural damage are negative prognostic factors that increase the risk of progression in AS. Anti-TNF medications have been demonstrated to prevent the progression of radiographic damage after four years. Secukinumab, on the other hand, has been shown to stop radiographic damage after two years of treatment (49, 50). Due to the lack of definitive data, the panel suggested

that patients with unfavorable prognostic factors should have the option between anti-TNF and anti-IL-17 therapies (Table III).

DISCUSSION AND CONCLUSIONS

RMDs are characterized by substantial heterogeneity in clinical manifestation and therapeutic response. The current vision of modern rheumatology points toward a precision medicine approach, possibly guided by genetic profiling of the individual patient or groups of patients, which enables the identification of the optimal drug for each individual patient. Despite these expectations, the selection of biotechnological drugs to date appears to be primarily, if not entirely, based on empirical selection criteria and economic factors. Numerous Italian regions have gradually restricted the prescribing freedom of individual rheumatologists, frequently imposing a dominant pharmacoeconomic perspective. Specifically, payers, clinicians, and patients lacked a coordinated strategy. Defining shared rules would permit prescriptive freedom and uniformity of therapeutic approach in accordance with pharmaceutical and economic considerations, but within the broader and more robust context of evidence-based medicine. The fragmentation of prescribing regulations across Italy's various regions may result in unequal access to care for patients based on their geographical location. This paper describes a virtuous process between rheumatologists and local healthcare system stakeholders that resulted in shared recommendations for prescribing the first biotechnological/small molecule drug to patients with RMD who had not previously been exposed to these medications. These pragmatic statements, which resulted from a Delphi-type approach applied to daily clinical issues, made it possible to clearly define, based on the available evidence, in which patients' biosimilar anti-TNF drugs should be used and when other mechanisms of action should be preferred. The pillars of any discussion on therapeutic algorithms for the treatment of RMD are international guidelines. However, these guidelines, which place all mechanisms of action on an equal footing, do not always help the clinician make a decision when confronted with particular clinical conditions of disease expression or comorbidities. The statements, which have become the subject of an official resolution of the Campania region, are the first attempt in Italy to share therapeutic strategies. This work has enabled the standardization of prescribing attitudes in Campania. Considering the recent extension of the right to prescribe bDMARD and tsDMARDs from selected hospital centers to all rheumatologists employed by the Regional Health System, this issue was even more pressing. This regulatory change will increase access to care and decrease therapeutic delay, but it may also increase prescription heterogeneity in the region. Our work also aims to reduce the rate of therapeutic failure as much as possible, resulting in a higher rate of clinical remission, employability, and global health, considering the financial impact on the health care system. Notably, this clinical guidance is strongly influenced by the limited availability of data informing the clinician on the likelihood of response to the treatment, and a trial-and-error approach is still prevalent in the field of rheumatology. The rheumatology community is still awaiting the use of clinical or biological predictors to guide the selection of the most appropriate treatment for each patient. In the meantime, this guidance will aid both expert and inexperienced clinicians in addressing the clinical challenges that the management of complex patients may present, thereby contributing to the reduction of heterogeneity and disparity in access to treatment for RMD patients.

Conflict of interest
The authors declare no potential conflict of interest.

REFERENCES

1. Kim JH, Choi IA. Cardiovascular morbidity and mortality in patients with spondyloarthritis: A meta-analysis. Int J Rheum Dis. 2021; 24: 477-86.
2. Provan SA, Lillegraven S, Sexton J, et al. Trends in all-cause and cardiovascular mortal-

ity in patients with incident rheumatoid arthritis: A 20-year follow-up matched case-cohort study. Rheumatol (United Kingdom). 2020; 59: 505-12.
3. Giacomelli R, Afeltra A, Bartoloni E, et al. The growing role of precision medicine for the treatment of autoimmune diseases; results of a systematic review of literature and Experts' Consensus. Autoimmun Rev. 2021; 20.
4. Kay J. Overcoming barriers to biosimilars in inflammatory arthritis. Nat Rev Rheumatol. 2020; 16: 65-66.
5. Alten R, Cronstein BN. Clinical trial development for biosimilars. Semin Arthritis Rheum. 2015; 44: S2-S8.
6. Ottaviani S, Gardette A, Roy C, et al. Body mass index and response to rituximab in rheumatoid arthritis. Jt Bone Spine. 2015; 82: 432-6.
7. Gremese E, Carletto A, Padovan M, et al. Obesity and reduction of the response rate to anti-tumor necrosis factor α in rheumatoid arthritis: An approach to a personalized medicine. Arthritis Care Res. 2013; 65: 94-100.
8. Iannone F, Courvoisier DS, Gottenberg JE, et al. Body mass does not impact the clinical response to intravenous abatacept in patients with rheumatoid arthritis. Analysis from the 'pan-European registry collaboration for abatacept (PANABA). Clin Rheumatol. 2017; 36: 773-9.
9. Channual J, Wu JJ, Dann FJ. Effects of tumor necrosis factor-α blockade on metabolic syndrome components in psoriasis and psoriatic arthritis and additional lessons learned from rheumatoid arthritis. Dermatol Ther. 2009; 22: 61-73.
10. Costa L, Caso F, Atteno M, et al. Impact of 24-month treatment with etanercept, adalimumab, or methotrexate on metabolic syndrome components in a cohort of 210 psoriatic arthritis patients. Clin Rheumatol. 2014; 33: 833-9.
11. Ruscitti P, Masedu F, Alvaro S, et al. Anti-interleukin-1 treatment in patients with rheumatoid arthritis and type 2 diabetes (TRACK): A multicentre, open-label, randomised controlled trial. PLoS Med. 2019; 16: 1-22.
12. Cock D De, Hyrich K. Malignancy and rheumatoid arthritis: Epidemiology, risk factors and management. Best Pract Res Clin Rheumatol. 2018; 32: 869-86.
13. Wadström H, Frisell T, Askling J. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, tocilizumab, abatacept, or rituximab in clinical practice: A nationwide cohort study from Sweden. JAMA Intern Med. 2017; 177: 1605-12.
14. Atzeni F, Carletto A, Foti R, et al. Incidence of cancer in patients with spondyloarthritis treated with anti-TNF drugs. Jt Bone Spine. 2018; 85: 455-9.
15. Hellgren K, Dreyer L, Arkema EV, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: A collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis. 2017; 76: 105-11.
16. Fagerli KM, Kearsley-Fleet L, Mercer LK, et al. Malignancy and mortality rates in patients with severe psoriatic arthritis requiring tumour-necrosis factor alpha inhibition: results from the British Society for Rheumatology Biologics Register. Rheumatol (United Kingdom). 2019; 58: 80-5.
17. Luo X, Deng C, Fei Y, et al. Malignancy development risk in psoriatic arthritis patients undergoing treatment: a systematic review and meta-analysis. Semin Arthritis Rheum. 2019; 48: 626-31.
18. Hellgren K, Ballegaard C, Delcoigne B, et al. Risk of solid cancers overall and by subtypes in patients with psoriatic arthritis treated with TNF inhibitors - a Nordic cohort study. Rheumatology (Oxford). 2021; 60: 3656-68.
19. Regierer AC, Strangfeld A. Rheumatoid arthritis treatment in patients with a history of cancer. Curr Opin Rheumatol. 2018; 30: 288-94.
20. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum. 2002; 46: 2294-300.
21. Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2015; 29: 290-305.
22. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: Meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis. 2009; 68: 25-32.
23. Chen SK, Liao KP, Liu J, Kim SC. Risk of hospitalized infection and initiation of abatacept versus tumor necrosis factor inhibitors among patients with rheumatoid arthritis: a propensity score-matched cohort study. Arthritis Care Res. 2020; 72: 9-17.
24. Minozzi S, Bonovas S, Lytras T, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf. 2016; 15: 11-34.
25. Haddad A, Li S, Thavaneswaran A, Cook RJ, Chandran V, Gladman DD. The incidence and predictors of infection in psoriasis and psoriatic arthritis: results from longitudinal observational cohorts. J Rheumatol. 2016; 43: 362-6.
26. Zabotti A, Goletti D, Lubrano E, Cantini F. The impact of the interleukin 12/23 inhibitor ustekinumab on the risk of infections in patients with psoriatic arthritis. Expert Opin Drug Saf. 2020; 19: 69-82.
27. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. Br J Dermatol. 2017; 177: 47-62.

28. Tsuboi H, Matsumoto I, Hagiwara S, et al. Effectiveness of abatacept for patients with Sjögren's syndrome associated with rheumatoid arthritis. An open label, multicenter, one-year, prospective study: ROSE (Rheumatoid Arthritis with Orencia Trial toward Sjögren's syndrome Endocrinopathy) trial. Mod Rheumatol. 2016; 26: 891-9.
29. Verstappen GM, Nimwegen JF van, Vissink A, Kroese FGM, Bootsma H. The value of rituximab treatment in primary Sjögren's syndrome. Clin Immunol. 2017; 182: 62-71.
30. Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: A systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020; 79: S760-70.
31. d'Alessandro M, Perillo F, Metella Refini R, et al. Efficacy of baricitinib in treating rheumatoid arthritis: Modulatory effects on fibrotic and inflammatory biomarkers in a real-life setting. Int Immunopharmacol. 2020; 86: 1-5.
32. Kurata I, Tsuboi H, Terasaki M, et al. Effect of biological disease-modifying anti-rheumatic drugs on airway and interstitial lung disease in patients with rheumatoid arthritis. Intern Med. 2019; 58: 1703-12.
33. Vadillo C, Nieto MA, Romero-Bueno F, et al. Efficacy of rituximab in slowing down progression of rheumatoid arthritis-related interstitial lung disease: Data from the NEREA Registry. Rheumatol (United Kingdom). 2020; 59: 2099-108.
34. Coates LC, Kavanaugh A, Mease PJ, et al. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol. 2016; 68: 1060-71.
35. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020; 79: S700-12.
36. Dreyer L, Magyari M, Laursen B, Cordtz R, Sellebjerg F, Locht H. Risk of multiple sclerosis during tumour necrosis factor inhibitor treatment for arthritis: A population-based study from DANBIO and the Danish Multiple Sclerosis Registry. Ann Rheum Dis. 2016; 75: 785-6.
37. Clowse ME, Förger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: Results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis. 2017; 76: 1890-6.
38. Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: Results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2018; 77: 228-33.
39. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020; 79: S685-99.
40. Lee YH, Song GG. Relative efficacy and safety of tofacitinib, baricitinib, upadacitinib, and filgotinib in comparison to adalimumab in patients with active rheumatoid arthritis. Z Rheumatol. 2020; 79: 785-96.
41. Baraliakos X, Gossec L, Pournara E, et al. Secukinumab in patients with psoriatic arthritis and axial manifestations: Results from the double-blind, randomised, phase 3 MAXIMISE trial. Ann Rheum Dis. 2021; 80: 582-90.
42. Mourad A, Gniadecki R. Treatment of dactylitis and enthesitis in psoriatic arthritis with biologic agents: A systematic review and meta-analysis. J Rheumatol. 2020; 47: 59-65.
43. Araujo EG, Englbrecht M, Hoepken S, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: Results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. Semin Arthritis Rheum. 2019; 48: 632-7.
44. Mease PJ, Smolen JS, Behrens F, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis 2020; 79: 123-31.
45. McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet (London, England). 2020; 395: 1496-505.
46. Reich K, Sullivan J, Arenberger P, et al. Effect of secukinumab on the clinical activity and disease burden of nail psoriasis: 32-week results from the randomized placebo-controlled TRANSFIGURE trial. Br J Dermatol. 2019; 181: 954-66.
47. Wasel N, Thaçi D, French LE, et al. Ixekizumab and ustekinumab efficacy in nail psoriasis in patients with moderate-to-severe psoriasis: 52-week results from a phase 3, head-to-head study (IXORA-S). Dermatol Ther (Heidelb). 2020; 10: 663-70.
48. Heijde D Van Der, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017; 76: 978-91.
49. Braun J, Baraliakos X, Deodhar A, et al. Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4-year results from the MEASURE 1 study. Rheumatol (United Kingdom). 2019; 58: 859-68.
50. Sari I, Haroon N. Disease modification in axial spondyloarthritis. Best Pract Res Clin Rheumatol. 2018; 32: 427-39.