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Safety of treatment options for spondyloarthritis: a narrative review

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Abstract

Introduction: Spondyloarthritis (SpA) are chronic inflammatory diseases with overlapping pathogenic mechanisms and clinical features. Treatment armamentarium against SpA includes non-steroidal anti-inflammatory drugs, glucocorticoids, conventional disease-modifying antirheumatic drugs (DMARDs, including sulfasalazine, methotrexate, leflunomide, cyclosporine), targeted synthetic DMARDs (apremilast) and biological DMARDs (TNF inhibitors, anti-IL 12/23 and anti-IL-17 agents).

Areas covered: A narrative review of published literature on safety profile of available SpA treatment options was performed. Readers will be provided with a comprehensive overview on frequent and rare adverse events associated with each drug listed in current SpA treatment recommendations.

Expert opinion: The overall safety profile of such molecules is good and serious adverse events are rare but need to be promptly recognized and treated. However, the monitoring of adverse events is a major challenge for clinicians because it is not adequately addressed by current treatment recommendations. A tailored treatment is crucial and rheumatologists must accurately select patients in order to identify those more susceptible to develop adverse events.

Keywords

Ankylosing spondylitis, biologics, DMARDs, NSAIDs, psoriatic arthritis, safety, spondyloarthritis.

1. Introduction

Spondyloarthritis (SpA) is a group of chronic inflammatory diseases with overlapping pathogenic mechanisms and clinical features including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis related to inflammatory bowel disease (IBD), the juvenile onset form and forms that not satisfy any definite criteria and referred as undifferentiated SpA (uSpA). Clinical features comprise inflammatory back pain (IBP), asymmetrical peripheral oligoarthritis, enthesitis, and other extra-articular manifestations such as anterior uveitis, psoriasis and IBD [1-3].

According to the classification criteria developed by the Assessment in SpondyloArthritis international Society (ASAS), SpA patients can be split into axial SpA (axSpA), with predominant involvement of spine and/or sacroiliac joints, and peripheral SpA (pSpA), with predominant peripheral involvement such as arthritis and/or enthesitis and/or dactylitis [4-6]. Peripheral SpA can include SpA related to IBD, ReA, uSpA, and PsA. However, in early PsA, the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria [7-9] work better than the ASAS ones [10].

Treatment of SpA must be planned according to recommendations proposed by international organisms such as European League Against Rheumatism (EULAR), ASAS and Group for Research and Assessment of Psoriasis and PsA (GRAPPA) [11-18].

In this narrative review we analyzed the safety profile of current SpA treatment options.

2. Treatment recommendations for axSpA

First line therapy for axSpA patients with pain and stiffness are non-steroidal anti-inflammatory drugs (NSAIDs) or selective COX-2 inhibitors (COXIBs). There is no evidence to support the efficacy of disease-modifying antirheumatic drugs (DMARDs), including sulfasalazine (SSZ) and methotrexate (MTX), for the treatment of axial disease. SSZ may be considered in patients with peripheral arthritis.

In patients with persistently high disease activity despite NSAIDs treatment, biological DMARDs are recommended. Current practice is to start with an anti-TNF agent [18] but there is no evidence

for a differential efficacy between the various TNF inhibitors on the axial and peripheral manifestations. If anti-TNF therapy fails, switching to another anti-TNF agent or IL-17 inhibitor therapy should be considered [18].

3. Treatment recommendations for pSpA, especially for PsA

Latest EULAR recommendations for pharmacological therapy of PsA comprise 5 overarching principles and 10 recommendations concerning NSAIDs, conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARD) and biological DMARDs (bDMARDs) including originator or biosimilar TNF inhibitors, anti-IL 12/23 and anti-IL-17 agents [14]. GRAPPA recommendations consider both dermatological and musculoskeletal manifestations and are organized into 6 domains (peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail involvement) based on the predominant involvement [15].

MTX is the first csDMARD recommended by EULAR in patients suffering from peripheral arthritis. For converse, SSZ, leflunomide (LEF) and cyclosporine (CSA) are considered only when MTX is contraindicated or has failed. On the other hand, GRAPPA recommends MTX, SSZ, or LEF as first csDMARD without a clear preference.

In patients with peripheral arthritis and an inadequate response to at least one csDMARD, a bDMARD - usually a TNF inhibitor - should be initiated according to the EULAR recommendations. If TNF inhibitors are not appropriate, hence bDMARDs targeting IL12/23 or IL17 pathways may be considered. In patients in whom bDMARDs are not appropriate, tsDMARDs - such as the phosphodiesterase 4 (PDE4) inhibitor apremilast (APR) - may be considered. On the contrary, GRAPPA experts place TNF inhibitors, other bDMARDs, and PDE4 inhibitors together as a first choice in PsA patients with an inadequate response to at least one csDMARD.

Both GRAPPA and EULAR suggest an early usage of bDMARD in patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections. A similar approach is suggested for patients with predominantly axial disease and insufficient response to

NSAIDs.

4. Current axSpA and PsA treatment - safety issues

Drugs approved for axSpA treatment are NSAIDs/COXIBs, originator and biosimilar TNF inhibitors, and the IL-17 blocker secukinumab (SEC).

Pharmacologic therapy for PsA includes NSAIDs, csDMARDs (MTX, SSZ, LEF and CSA), local glucocorticoids injections, systemic administration of glucocorticoids, tsDMARD (APR), originator and biosimilar TNF inhibitors, SEC and the IL-12/23 inhibitor ustekinumab (UST).

Safety data reported in main clinical trials are summarized in table 1.

4.1 NSAIDs/COXIBs

A recent review of randomized controlled trials (RCTs) investigated differences in NSAIDs safety when used for axSpA over a period of 12 weeks [19]. The study concluded that all analysed NSAIDs (including COXIBs) have no more associated adverse effects than placebo over 12 weeks.

In 2011, a systematic review on safety of NSAIDs in patients receiving MTX for inflammatory arthritis showed no evidence of increased risk of MTX-induced pulmonary disease and impairment of renal and liver function [20].

In 2012, Poddubnyy and van der Heijde analyzed therapeutic controversies regarding NSAIDs in SpA [21]. They found that the most common adverse events related to NSAIDs therapy were gastrointestinal and cardiovascular ones. Three trials comparing COXIBs with nonselective NSAIDs showed a higher rate of serious gastrointestinal events (symptomatic gastric or duodenal ulcers and related complications) for nonselective NSAIDs [22-24]. These data originated from RCTs including rheumatoid arthritis and osteoarthritis patients. However, in 3 long-term NSAID trials enrolling AS patients, no additional toxicity signals were reported and adverse events incidence - or discontinuations due to adverse events - did not significantly differ within treatment groups [21, 25-27].

In a meta-analysis of RCTs, a moderately elevated risk of adverse cardiovascular and gastrointestinal events was found in patients receiving NSAIDs except for naproxen that did not increase cardiovascular risk [28]. Nevertheless, relative risk of cardiovascular or gastrointestinal adverse events was lower in young patients and in those without known cardiovascular or gastrointestinal risk factors who represent the vast majority of SpA patients [29].

In a Swedish population-based cohort study on 21,872 patients with AS or SpA, no differences in serious cardiovascular, gastrointestinal, or renal adverse events risk among 3 exposure groups (etoricoxib, celecoxib and nonselective NSAIDs) were found [30].

Moreover, in an observational study on AS patients from Norway, the infrequent use of NSAIDs was associated with an increased overall mortality [31]. Similar data were found in a population-based retrospective study from Canada showing a reduced cardiovascular risk in AS patients taking NSAIDs [32].

4.2 Glucocorticoids

Systemic glucocorticoids are not recommended in axSpA according to ASAS/EULAR recommendations [18], and may be used with caution at the lowest effective dose in PsA according to EULAR recommendations [14]. However, despite there are no evidence from RCTs, systemic glucocorticoids are commonly used to treat PsA patients who are poorly responsive to NSAIDs or DMARDs [12, 33].

According to international recommendations [14, 15, 18], intra-articular and local glucocorticoids injections should be used to treat peripheral arthritis, dactylitis and enthesitis in PsA and SpA, taking care to avoid psoriatic lesions, and Achilles, patellar or quadriceps tendons due to risk of tendon rupture.

In a review by Habib and colleagues [34], local side effects of intra-articular glucocorticoids injections included intra-articular and periarticular calcifications, skin atrophy or depigmentation, avascular necrosis, rapid destruction of the femoral head, acute synovitis, Charcot's arthropathy,

tendinopathy, Nicolau's syndrome, and joint dislocation.

In clinical practice, risks of glucocorticoids injections are mainly related to discomfort of the procedure, post-injection pain and flushing [35]. Most feared adverse event is septic arthritis which is estimated to occur in about 1 out of 10.000 injections. In a French study, 15 cases of sepsis occurred after 1.160.000 local glucocorticoids injections but 9 of these were related to the use of glucocorticoids not packaged in a sterile syringe [36].

4.3 csDMARDs

In 2008, a review by Ravindran and colleagues compared efficacy and toxicity of csDMARDs in PsA. Regarding toxicity, withdrawal due to LEF was more common (RR=3.86; 95% CI 1.2, 12.39; p=0.02) compared to SSZ (RR=1.76; 95% CI 0.98, 3.14; p=0.06); ratio of numbers needed to treat (NNT) to numbers needed to harm (NNH) was 0.93 for SSZ and 0.45 for LEF [37]. In 2012, another systematic review on csDMARDs safety in PsA found that the global risk of withdrawals due to adverse events was 2.41 (95% CI 1.53, 3.82) [38].

4.3.1 Methotrexate

MTX is generally used in a single weekly parenteral (intramuscular or subcutaneous) or oral dose, ranging from 7.5 to 25 mg. Toxicity is mainly characterized by nausea, vomiting, diarrhoea, fatigue, stomatitis, headache, alopecia, chills and fever, photosensitivity, dizziness, interstitial pneumonitis, anemia, leukopenia, thrombocytopenia and elevation of liver function test (LFT) [39]. Major adverse events include birth defects, bone marrow toxicity, hepatotoxicity and pulmonary fibrosis. Low dose folate supplementation may reduce hematologic, hepatic and gastrointestinal side effects without decreasing efficacy [40]. Many studies suggested that liver toxicity may be more relevant in PsA than RA. A meta-analysis of serial liver biopsy studies found higher rates of fibrosis in psoriasis patients than in RA, partly related to alcohol use [41]. Furthermore, in PsA patients, obesity, diabetes, non-alcoholic fatty liver disease or alcoholism, may work in concert with MTX to increase the susceptibility to liver toxicity. Data registries analysis, wherein some comparison can

be made between PsA and RA cohorts - such as NOR-DMARD or CORRONA - suggests that LFT elevation is more frequently observed in PsA [42-43].

MTX is primarily eliminated via kidney excretion, and should be used with caution in patients with renal insufficiency. MTX is absolutely contraindicated during pregnancy or breastfeeding, and in patients with cirrhosis, leukopenia, anemia or thrombocytopenia. MTX should be withdrawn 3 months before conception due to proven teratogenicity [44].

In the Methotrexate in PsA (MIPA) RCT, 109 patients taking MTX were compared to 112 patients treated with placebo and observed over a period of 6 months. In patients receiving MTX, adverse events were the main reason for withdrawal in 9 patients and the secondary reason in 2. Common adverse events (> 5% per arm) included nausea and vomiting (38 patients receiving MTX, 16 patients receiving placebo), respiratory tract infections (31 MTX, 25 placebo), abdominal pain (16 MTX, 6 placebo) and abnormal LFT (12 MTX, 2 placebo) [45].

A systematic literature review of long-term safety of MTX monotherapy in RA found that the rate of discontinuation for toxicity in the MTX groups ranged from 10 to 37% and most common adverse events were gastrointestinal and LFT elevation. Moreover, MTX showed a reduced cardiovascular mortality in comparison with RA patients treated with other csDMARDs [46].

In 2016, Costa and colleagues published an observational study focused on incidence of malignancies in a cohort of 618 PsA patients taking csDMARDs and TNF inhibitors. During a median follow-up of 9 years, 44 patients (7.1%) had a diagnosis of malignancy, of which 14 were receiving TNF inhibitors and 30 csDMARDs. There were no differences between the 2 treatment groups and the only predictor of malignancy occurrence was age [47].

4.3.2 Sulfasalazine

SSZ is used to treat IBD, PsA and SpA with peripheral involvement. Adverse effects occur in many patients but are mild and include gastrointestinal side effects (nausea, heartburn, vomiting, diarrhoea, anorexia and LFT elevation), headache, pruritus, urticaria, malaise, fever, reversible oligospermia and rash. Serious adverse events - including neutropenia, aplastic anaemia,

agranulocytosis and haemolysis - are rare.

In a meta-analysis of efficacy and toxicity of csDMARDs for PsA, withdrawal due to drug toxicity was relatively high (RR=1.76; 95% CI 0.98, 3.14; p=0.06), while the NNT/NNH ratio was 0.93 [37]. In a recent systematic review and meta-analysis comparing SSZ and placebo for adverse events, the risk of withdrawal due to adverse events ranged from 0.94 to 7.39 for gastrointestinal symptoms, from 0.23 to 6.23 for cutaneous symptoms and from 0.4 to 3.1 for liver dysfunctions [38]. In a Cochrane systematic review on SSZ compared to placebo in AS, a significantly higher rate of withdrawals due to adverse effects (RR 1.50, 95% CI 1.04 to 2.15) was found in the SSZ group. Only 1 serious adverse reaction was reported in patients taking SSZ [48].

According to EULAR recommendations, SSZ is compatible with pregnancy and lactation and should be considered for continuation [44].

4.3.3 Leflunomide

The most common side effects caused by LEF are gastrointestinal (diarrhoea, dyspepsia, abdominal pain, nausea, elevation of LFT), but include also hypertension, reversible alopecia, drug eruptions, pruritus, dizziness, headache, leukopenia, increased risk of infection, and teratogenicity. Liver injury occurs mostly within the first 6 months of therapy and in patients with multiple risk factors for hepatotoxicity [39]. Efficacy and safety of LEF in PsA have been evaluated in a RCT in 2004 [49], in which most common adverse events were diarrhoea and reversible LFT elevation with no cases of sever liver toxicity.

In the meta-analysis by Ravindran and colleagues, toxicity leading to withdrawal was most common with LEF (RR=3.86; 95% CI 1.2, 12.39; p=0.02), but the NNT/NNH ratio was only 0.45 [37]. Pereda and colleagues found in their meta-analysis an OR of 5.11 for adverse events with LEF compared to placebo; risk of withdrawal due to gastrointestinal symptoms was 1.66 (0.90-3.06), 0.95 (0.40-2.24) for flu syndrome, 1.89 (0.82-4.35) for cutaneous symptoms, 2.49 (0.84-7.36) for liver dysfunction and 1.57 (0.58-4.25) for headache [38].

Other data on LEF come from a large European prospective observational study by Behrens et al.

[50]. Adverse events occurred in 62 (12.1%) patients, mostly diarrhoea (16.3%), alopecia (9.2%), hypertension (8.2%), and pruritus (5.1%). Three adverse events were serious (2 of LFT increase, 1 hypertensive crisis), and 2 out of 3 resolved at the end of the study. There were no deaths during the 24-weeks study, and adding LEF to concomitant csDMARD therapy did not lead to an increased risk of adverse events [50]. Similar data on safety profile of LEF in active AS were found in an open label trial [51] and a double blind, randomised, placebo-controlled study [52].

The drug should be avoided in pregnancy and in lactating women and a wash-out procedure should be completed before conception [44].

4.3.4 Cyclosporine

The most frequent side effects of CSA are nephrotoxicity and hypertension. Patients treated continuously for more than 2 years have a higher risk of developing irreversible renal injury; for shorter term treatment renal damage is generally reversible. New-onset arterial hypertension incidence ranges from 0 to 57% across many studies and is more common in elderly patients. Elevation of serum triglycerides and hypercholesterolemia occurs in up to 15% of patients. Headache, paresthesia, tremor, fatigue and sleep disturbances can develop in up to 40% of patients. Hypertrichosis can occur in up to 60% of patients. Other side effects are gingival hypertrophy, asthenia, cough, rhinitis, abdominal pain, nausea, hyperuricemia, hypomagnesemia, and rare psychiatric side effects [39, 53].

In the meta-analysis of Ravindran et al. [37] – based mainly on the study of Fraser [54] - overall toxicity estimated on withdrawals due to side effects was 3.88 (Peto OR 95% CI 1.08-13.92). In the systematic review of Pereda et al., the risk of withdrawal due to gastrointestinal symptoms was 3.04 (1.02-9.10), 6.8 (0.34-136.64) for cutaneous symptoms was and 4.97 (0.99-24.90) for headache [38]. In a 24 week, prospective, randomized, open study in active PsA patients, mild and reversible kidney dysfunction was the most common adverse event [55]. In a long term prospective, non-randomised study of 60 CSA-treated PsA patients, adverse effects included hypertrichosis (24%), hypertension (21%), nephrotoxicity (17%), gingival hyperplasia (12%), gastrointestinal intolerance

(9%) and neurological disturbance (7%); 7 patients withdrew due to side effects (2 for severe gingival hyperplasia, 2 for hypertension, 2 for hypertrichosis and 1 for neurological disturbances). No elevation of LFT and no major infectious complications attributable to CSA were recorded during the study [56].

Addition of CSA to ETN in PsA patients with uncontrolled cutaneous disease resulted to be a safe and effective therapeutic option [57], although not currently recommended by EULAR [14].

In a 1-year prospective study on 225 patients with PsA, CSA alone - or in combination with other csDMARDs - did not induce a reactivation of commonly tested viruses [58]. Furthermore, CSA has been shown to suppress replication of HCV both in vitro and in vivo, and can be safely administered in HCV patients [53].

Risk of neoplastic diseases, especially non-melanoma skin cancer, in patients with PsA and psoriasis who are taking CSA, has been considered related to psoralen (P) and ultraviolet A (UVA) therapy [39, 47]. There is no evidence that CSA predisposes to solid malignancies; large controlled studies have even suggested an immunoprotective action of CSA with a decreased risk for breast and colon cancers [53, 59].

CSA can be continued throughout pregnancy at the lowest effective dose. CSA is compatible and should be considered for continuation during breast-feeding, if newborn does not present contraindicating conditions [44].

4.4 tsDMARD

4.4.1 Apremilast

APR is an oral PDE4 inhibitor approved for PsA and psoriasis treatment. One phase II trial in AS patients and 4 phase III trials in PsA patients evaluated efficacy and safety of APR. The first study enrolled 36 AS patients, observed over a 12-week period and then for a 4-week follow-up for safety and clinical assessments. Incidence of side effects, mainly mild in intensity, was similar in the two treatment arms (94.7% APR, 89.5% placebo). Two APR patients withdrew due to diarrhoea and

daze, respectively. Compared to placebo, APR patients had a higher incidence of headaches (26.3% versus 42.1%) and loose stools (10.5% versus 26.3%) [60].

A recent meta-analysis evaluated 4 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies on clinical efficacy and safety of APR in PsA [61]. An overall number of 2.015 patients were enrolled in PALACE 1-4 trials and were randomized to receive APR 20 mg or APR 30 mg or placebo twice daily during the 24-week placebo-controlled phase. Incidence of serious adverse events was low for all 4 trials, with no statistically significant differences. Most common side effects were diarrhoea, nausea, upper respiratory tract infections, infestation and nervous system disorders (mainly headache). Incidence of adverse events occurring in APR group was statistically higher than placebo (OR 2.64, $p<0.00001$ for APR 20 mg; OR 4.59, $p<0.00001$ for APR 30 mg), but all the events were well tolerated and did not lead to drug discontinuation.

Long-term (104 weeks) data from PALACE1 showed reducing incidence of gastrointestinal adverse events with continued APR treatment [62]. Diarrhoea was reported in 19.2% of patients in APR 30 mg group at 52 weeks and only in 1.8% of patients at 104 weeks. Weight loss was reported in a small proportion of patients during both the placebo-controlled period (placebo: 0.4%; APR 20 mg bid: 1.0%; APR 30 mg bid: 1.4%) and longer APR periods (APR 20 mg bid: 1.4%; APR 30 mg bid: 1.8% through week 52); the majority of patients remaining within 5% of baseline weight throughout the 52 weeks of the study [62, 63].

New important advice regarding suicidal ideation and behaviour came from European Medicines Agency in October 2016. Although suicidal behaviour-related events and depression are more common in patients with psoriasis and PsA than in the general population, evidence from clinical trials and post-marketing experience suggests a causal association between suicidal ideation and the use of APR [64]. Therefore, the risks and benefits of starting or continuing treatment with APR should be carefully assessed if patients presenting previous or current psychiatric symptoms.

There are limited data about APR use in pregnant and breast-feeding women; accordingly APR is currently contraindicated during pregnancy and lactation.

4.5 bDMARDs

4.5.1 TNF inhibitors

Data on safety of anti-TNF in PsA and AS come from RCTs, observational open-label extensions of RCTs, meta-analyses and registers.

A systematic review of RCTs focused on short-term efficacy and safety of infliximab (IFX), etanercept (ETN), adalimumab (ADA) and golimumab (GOL) in AS patients has been recently published [65]. This study found an increased risk of withdrawal due to adverse events in the anti-TNF group compared to placebo (OR 2.44, 95% CI 1.26 to 4.72; total events: 38/1637 in biologic group; 7/986 in the placebo group) without any additional risk of serious adverse events (OR 1.45) [65].

In a meta-analysis of Ravindran and colleagues, withdrawal as a result of TNF inhibitor-related toxicity was higher compared to placebo but not reaching statistical significance (RR 2.2; p=0.12); furthermore, TNF inhibitors had the better NNT/NNH (0.25) compared to csDMARDs [37].

In a systematic review and meta-analysis on the efficacy and safety of ADA, ETN, GOL and IFX in PsA patients, including 9 RCTs and 6 observational studies, no difference in the occurrence of adverse events and serious adverse events between anti-TNF and control groups was found [66]. Similarly, in the study by Fénix-Caballero and colleagues, the most frequent adverse event was upper-airway infections [67].

Development of malignancies related to anti-TNF treatment is a debated topic. In an observational study by Costa et al., a total of 618 PsA patients were included and 296 of them were taking anti-TNF agents. This study found that the only predictor of malignancy occurrence was increasing age [47]. In a collaborative study from the ARTIS and DANBIO registers including 8.703 SpA patients, anti-TNF treatment was not associated with an increased risk of cancer and results were comparable for AS and PsA when analysed separately [68]. Similar data were found in an overview of systematic reviews and meta-analyses of RCTs evaluating malignancy risk of anti-TNF medications

[69].

TNF inhibiting therapy is associated with an increased risk of tuberculosis (TB) reactivation since TNF is a key player in the immune response against mycobacteria. Many studies showed an increased risk of developing TB in patients treated with IFX or ADA compared to ETN. In a recent review, risk of TB after TNF inhibitors therapy in patients with rheumatoid arthritis, AS and PsA receiving IFX, ADA and ETN was evaluated [70]. Ten TB cases occurred among 4590 patients in 16 RCTs of IFX, 9 among 7009 patients in 21 RCTs of ADA, and 4 among 7741 patients in 26 RCTs of ETN. Overall, 19/23 (83%) TB cases occurred in patients with rheumatoid arthritis. Data from national registries and post-marketing surveillance showed an increased risk of TB in patients receiving any of the 3 TNF inhibitors, with a 3-4 times higher risk associated with IFX and ADA compared to ETN. Up to 80% of the patients, however, presented some deviation from the recommended TB prevention procedures [70].

Pre-treatment screening requires a detailed medical history, interferon gamma release assay (IGRA) and/or tuberculin skin test and chest X-ray. In case of suspected latent TB infection, a prophylactic therapy with isoniazid must be initiated at least 4 weeks before starting therapy and continued for the following 6-9 months [71].

Reactivation of Varicella Zoster Virus (VZV) is described during TNF inhibitors therapy. The incidence rate of VZV reactivation using TNF inhibitors for AS, PsA and psoriasis was 4.4/1000 patients/year [72]. Several studies suggested that IFX increases the risk of VZV reactivation, whereas the effect of other biologics remains controversial. Some authors suggested considering VZV vaccination prior to initiation of biological therapy, particularly infliximab [73].

Reactivation of hepatitis B virus (HBV) can occur in patients carrying a chronic inactive infection (HBsAg-positive with persistently normal LFT and with HBV-DNA negative) or with a past HBV infection (HBsAg-negative and HBsAb-negative with anti-HBcAb positive) starting a TNF inhibitor therapy. In HBsAg positive individuals treated with anti-TNF agents but not with prophylactic antiviral therapy, the reactivation of HBV is estimated to occur in 39% of patients [71,

73]. Antiviral prophylactic therapy is recommended in HBsAg-positive patients, in HBsAg-negative and HBcAb-positive patients if HBV-DNA is present. Antiviral drugs with low resistance rate like tenofovir and entecavir should be preferred to lamivudine due to the long duration of treatment. The prophylactic therapy should be continued for 12-18 months after the TNF inhibitor discontinuation because HBV reactivation may occur weeks or months after the end of immunosuppression. HBV vaccination should be considered in HBsAb-negative patients. Recommended screening before starting treatment with anti-TNF agents requires HBsAg, anti-HBsAb IgG and IgM, anti-HBcAb IgG and IgM and HBV-DNA [71, 73].

Treatment with TNF inhibitors in hepatitis C virus (HCV) infection is generally considered safe but requires caution. Therefore, it is advisable to perform a pre-treatment screening with anti-HCV antibodies and HVC-RNA and continuous monitoring of HCV-RNA and LFT in positive patients [71, 73].

During anti-TNF treatment, inactivated influenza and pneumococcal vaccinations are strongly recommended, while tetanus toxoid vaccination should be administered as in the general population; for converse, live-attenuated vaccines should be avoided [71, 73].

TNF inhibitors, mainly IFX, showed a high risk of inducing new-onset or worsening of pre-existing congestive heart failure and should not be initiated in patients with New York Heart Association (NYHA) Grade 3 or 4 cardiac failure. However, long-term treatment with anti-TNF resulted to be associated with an overall reduction in cardiovascular risk [71-73].

TNF inhibitors seem to lead to a higher risk of demyelinating diseases; therefore, they are contraindicated in patients with a personal or familial history of multiple sclerosis and other demyelinating diseases [73].

Many patients with SpA can develop paradoxical effects during anti-TNF therapy such as occurrence of psoriatic lesions in PsA patients without previous skin involvement, or an exacerbation of the skin manifestations. Most commonly, skin involvement is represented by pustular lesions localized on palms and/or soles [71, 72]. Psoriasiform lesions induced by TNF

inhibitors have a prevalence ranging from 0.6 to 5.3% that exceeds the 1-2% expected by chance [74]. Less frequent paradoxical effects reported during treatment with TNF inhibitors (mainly with etanercept) include uveitis and IBD [72].

TNF inhibitors continuation should be considered during the first part of pregnancy and during breast feeding [44].

4.5.1.1 Infliximab

IFX is a chimeric monoclonal antibody targeting soluble and membrane-bound TNF administered at weeks 0, 2, and 6 and every 8 weeks thereafter at a dosage of 5 mg/kg [75].

Side effects reported with IFX therapy are infusion reactions, infections including sepsis and TB, development of antibodies to IFX or antinuclear antibodies, congestive heart failure, demyelinating or new autoimmune disorders and malignancies.

In the review of Maxwell and colleagues, the RR of withdrawals due to adverse events in AS patients was 1.77 with an absolute increased harm of 0.5%. RR for serious adverse events was 2.53 with an absolute increased harm of 2.3% [65]. RR of withdrawals due to side effects in PsA patients receiving IFX ranged from 2.42 to 3.88 [37]. In the meta-analysis of Lemos et al, RR for adverse events, serious adverse events, injection-site reaction, discontinuation due to adverse events, discontinuation due to lack of efficacy were 1.16, 1.50, 1.12, 3.11, 0.50, respectively [66].

Data from national registries and post-marketing surveillance showed an incidence rate of TB reactivation ranging from 17 to 716 cases/100.000/year (median 284.5) in patients treated with IFX, with a significantly increased RR compared to the general population [70].

The risk of acute infusion reaction is estimated about 20% of patients, particularly in anti-infliximab antibodies positive patients [73].

4.5.1.2 Etanercept

ETN, a fully-human soluble TNF receptor, is a fusion protein composed of two extracellular domains of the human p75-TNF-receptor, linked to the Fc portion of human IgG1 administered subcutaneously at dose of 25 mg twice weekly or 50 mg once weekly [75, 76]. The main adverse

events reported during PsA and AS RCTs and respective open-label extension are injections site reactions, upper respiratory tract infections, rhinitis, diarrhoea, flu syndrome, headache, rash, urinary tract infections and sinusitis [76].

In the review of Maxwell and colleagues, withdrawal due to adverse events in ETN patients was increased compared to placebo with a RR 3.65 and absolute increased harm of 2%; for serious adverse events the RR was 1.69 with an absolute increased harm of 1% [65]. RR of withdrawal due to side effects in PsA patients ranged from 1.03 to 1.97 in the review of Ravindran et al. [37]. In the Lemos et al. meta-analysis RR for serious adverse events, injection-site reaction, discontinuation due to adverse events, discontinuation due to lack of efficacy were 0.86, 4.27, 1.03 and 0.21, respectively [66]. Globally, injection site reactions are estimated to occur in 36% of individuals treated [73].

An increased risk of active TB was found in all registries, with an incidence ratio ranging from 9.3 to 233 cases/100,000/year (median 85.5), lower than with ADA or IFX [70]. New-onset of IBD may also occur during ETN treatment [72].

ETN may be considered for use throughout pregnancy due to low rate of transplacental passage [44].

4.5.1.3 Adalimumab

ADA is a fully human anti-TNF monoclonal antibody administered subcutaneously at the dosage of 40 mg every 2 weeks [75]. Adverse events include injection site reactions, headache, infections (nasopharyngitis, pharyngitis, upper respiratory tract infection), TB and other opportunistic infections, malignancies and development of anti-drug antibodies.

In the review of Maxwell and colleagues, RR of withdrawals due to adverse events in ADA patients compared to placebo was RR 1.69 with an absolute increased harm of 0.6%. RR for serious adverse events was 0.92 with an absolute increased harm of -0.2% [65]. RR for withdrawals due to side effect in PsA patients receiving ADA in the review of Ravindran et al. was 2.95 [37]. In the meta-analysis of Lemos and colleagues, RR for adverse events, serious adverse events, injection-site reaction, discontinuation due to adverse events, discontinuation due to lack of efficacy were 0.84,

0.70, 1.44, 1.06 and 0.29, respectively [66]. Injection site reactions are reported in 15% of patients treated with ADA [73].

Data from registries showed an increased risk of active TB, with incidence rates ranging from 91 to 308 cases/100.000/year (median 203) [70].

4.5.1.4 Golimumab

GOL is a humanized IgG1k anti-TNF antibody given subcutaneously at the dosage of 50 mg every month [75].

The safety of GOL in AS patients and PsA patients was analysed in GO-RAISE study, GO-REVEAL study and their respective 5-years extension [77, 78]. In GO-RAISE, AS patients who died, with serious adverse event, who discontinued study agent due to adverse events, with malignancy, serious infections and with injection-site reaction were in 0.3%, 20.4%, 9.1%, 0.8%, 5.9% and 12.2%, respectively. All adverse events were more frequent in the GOL 100 mg dose group [77]. In GO-REVEAL study, PsA patients with serious adverse events, serious infections, injection site reactions, discontinuation due to adverse events, major cardiac events were in 21.1%, 3.8%, 9.4%, 12.4% and 2.8%, respectively. Adverse events were recorded more frequently in GOL 100 mg group [78].

In the review of Maxwell et al., RR of withdrawals due to adverse events was 1.97 with an absolute increased harm of 1.6%. RR for serious adverse events was 0.69 with an absolute increased harm of 0.5% [65]. In the meta-analysis of Lemos and colleagues, RR for adverse events, serious adverse events, injection-site reaction, discontinuation due to adverse events, discontinuation due to lack of efficacy were 1.14, 0.33, 1.03, 0.77 and 0.39, respectively [66]. Injection site reactions are reported in 5.8% of patients treated with GOL [73].

4.5.1.5 Certolizumab

Certolizumab pegol (CZP) is a PEGylated Fab fragment of a humanized TNF inhibitor monoclonal antibody administered subcutaneously 400 mg at week 0, 2 and 4 (loading dose) followed by 200 mg every 2 weeks.

CZP showed a good safety profile according to RCTs in patients with axSpA and PsA [79, 80]. In RAPID-axSpa trial, 315 patients received a dose of CZP through 96 weeks of follow up period. Most common side effect was non-serious infections. Serious adverse events occurred in 41 patients (13.0%). One case of active TB occurred, serious infections occurred in 3.8% of patients. No malignancies, demyelinating diseases or deaths were reported during the 96-weeks period [79].

In RAPID-PsA study, serious adverse events were 67 (12%) with the highest number reported for infection and infestation, with no cases of TB. The most common non-infectious adverse event was headache. Injection site reactions were more frequently observed in CZP group than in placebo group. The most common serious infections were pneumonia, HIV, urinary tract infections and erysipela. Thirty-six patients (9.2%) experienced an adverse event leading to withdrawal. During the 96-week trial period, 6 patients experienced an adverse event leading to death and 4 malignancies were reported. Antibodies to CZP were detectable in a few patients [80]. Injection site reactions are reported in 6.4% of patients treated with CZP [73].

The favourable tolerability profile was confirmed by a systematic review and meta-analysis where the main pooled risk ratios of CZP-treated patients versus control patients were the following: adverse events 1.09 (95% confidence interval, CI 1.04-1.14), serious adverse events 1.50 (95% CI 1.21-1.86), infectious AEs 1.28 (95% CI 1.13-1.45), serious infectious 2.17 (95% CI 1.36-3.47), injection-site reactions 1.59 (95% CI 0.63-3.99), upper respiratory tract infections 1.34 (95% CI 1.15-1.57) [81].

CZP may be considered for use throughout pregnancy due to low transplacental transfer and is compatible with breast-feeding [44].

4.5.2 Ustekinumab

UST is a human monoclonal antibody against IL-12 and IL-23, approved by European Medicines Agency (EMA) and Food and Drug Administration (FDA) for moderate to severe plaque psoriasis and active PsA. Efficacy and safety of UST in PsA have been evaluated in 2 large phase III trials, PSUMMIT 1 and PSUMMIT 2 [82, 83].

In PSUMMIT 1, 615 patients with no prior exposure to TNF inhibitors were randomized to receive UST 45 mg, UST 90 mg or placebo. At week 16, rates adverse events were similar in the UST and placebo groups (41.8% vs 42.0%). Most common adverse events in UST group were nasopharyngitis, upper respiratory tract infection, headache, arthralgia, nausea and diarrhoea. No opportunistic infections, TB, deaths or malignancies were reported by week 52. Only 18 patients discontinued the study for adverse events, while 9 patients had an injection-site reaction compared with 10 patients in the placebo group [82]. In PSUMMIT 1 extension study including 598 patients, followed through week 108, 23 patients discontinued UST due to adverse events and safety findings were consistent with those observed throughout week 52. Four malignancies, 11 serious infection and 7 major adverse cardiovascular events occurred. UST treatment did not appear to affect hematologic or chemistry laboratory findings [84].

Similar data were found in PSUMMIT 2 trial, where 312 patients with active PsA despite treatment with csDMARDs and/or TNF inhibitors were randomised to UST 45 mg or UST 90 mg or placebo. Adverse events and serious adverse events were similar in UST compared to placebo group; through week 60 no patients died, no cases of TB were reported and 1 case of septic shock related to Candida spp (identified in stool) was reported. By week 60, 1 bacteraemia, 2 malignancies (in TNF inhibitor-experienced patients) and 2 adjudicated events of myocardial infarction (in TNF inhibitor-experienced patients with established cardiovascular risk factors) were reported [83].

Long term safety data of UST come from the analysis of the PSOLAR registry. On a total of 12.093 psoriasis patients, no increased risk of malignancy, major adverse cardiac events, serious infections or mortality were found [85]. Similarly, in a long term safety evaluation of UST in patients 3.117 patients with moderate-to-severe psoriasis (858 with an history of PsA), rates of common and serious adverse events were generally consistent with, or lower than, those reported during the controlled period [86].

UST has limited evidence on usage during pregnancy and should be replaced before conception and avoided during lactation [44].

4.5.3 Secukinumab

SEC is a human IgG1 monoclonal antibody that neutralises IL-17A. Evidence of efficacy and safety of SEC in AS are provided in 1 phase II and 2 phase III trials. In 2013, Beaten et al. in a 28-weeks multicenter, randomized, double-blind, placebo-controlled clinical trial found, among 30 AS patients, only 1 serious adverse event in the treatment group [87]. In MEASURE 1 and MEASURE 2 trials, side effects rates in the SEC arms were similar in both studies; reported rates of grade 3 or 4 neutropenia, candida infections, and Crohn's disease were 0.7, 0.9, and 0.7 cases per 100 patient-years, respectively; exposure-adjusted pooled incidence rate for infections or infestation during the entire period was 68.8 (with SEC) and 63.8 (with placebo) per 100 patient-years. Most common side effects during the placebo-controlled period and the entire safety period were nasopharyngitis, headache and diarrhoea [88, 89]. In a long-term safety evaluation of SEC in AS patients in MEASURE 1, exposure-adjusted incidence rates for malignancy, major adverse cardiac events, IBD and serious infections were 0.6, 0.4, 0.8 and 1.0 per 100 patient-years, respectively; no cases of TB over the 2 years treatment were reported in MEASURE 1 [90, 91].

Safety profile of SEC in PsA has been assessed in 2 phase III trials [92, 93]. Among a mean exposure of 438.5 days in FUTURE 1 and 411.7 in FUTURE 2, exposure-adjusted incidence rate of any adverse event for SEC was 471 and 307 per 100 patient-years, respectively. Most common adverse events during the entire safety data reporting period were nasopharyngitis, headache and upper respiratory tract infections. Of note, SEC demonstrated a low potential for immunogenicity, with less than 1% of treated patients developing anti-drug antibodies [92-94]. In a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis, analysing data from 3993 subjects of which 3430 receiving SEC or ETN over 52 weeks, comparable incidence rates of total serious and non-serious adverse events were demonstrated [95]. In the 2-year efficacy and safety assessment of the FUTURE 1 study a similar incidence rate of AEs and SAEs was found at 104 weeks and 52 weeks, and overall incidence of adverse events with SEC had no dose-dependence [96].

There are no available data regarding the usage of SEC in pregnant and lactating women, accordingly its use should be avoided.

5. Expert opinion

The last two decades represented a turning point in SpA treatment thanks to the introduction of novel targeted biologic agents, particularly TNF blockers, which allow reducing signs and symptoms, improving physical function and quality of life measures in patients with active disease. Despite the key role of bDMARDs in the management of SpA is currently unquestionable, some points concerning safety issues need to be further clarified.

In the present article, we provided a broad overview on the safety of conventional and biological drugs licensed for treating SpA. The overall safety profile of such molecules is good and serious adverse events are rare but need to be promptly recognized and treated. Accordingly, a tailored approach is crucial and rheumatologists must select accurately patients in order to identify those more prone to develop adverse events.

The risk of cardiovascular and gastrointestinal adverse events associated with NSAIDs/COXIBs use seems to be lower in younger patients and in those without known predisposing factors, who represent the vast majority of SpA patients. Further, some studies showed that the increased cardiovascular risk associated with AS may be even reduced by using NSAIDs. This paradoxical phenomenon could be explained by the overall improvement in functional performance and systemic inflammation. For converse, in patients with increased gastrointestinal risk, a COXIBs or a non-selective NSAID plus a gastroprotective agent should be the treatment of choice.

There is no evidence to support a difference in efficacy of the various biological agents on axial or peripheral manifestations. Safety issues could drive the choice in selected patients i.e. patients with recurrent infections or those that are clearly prone to develop them, with IBD, with severe cardiac disorders or with demyelinating diseases.

TNF inhibitors were already on the market for a long time. Therefore, positive long-term safety data

from registries and rheumatologists' experience in clinical practice with such agents greatly outweighs that with SEC and UST, both in terms of volume and duration of follow-up.

In conclusion, the monitoring of adverse events is a major challenge for clinicians because it is not adequately addressed by current treatment recommendations. Since specific literature is scarce, we provide some tips about pre-treatment evaluation, major toxicity warnings, clinical and laboratory monitoring for each of the reviewed drugs (Table 2).

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Highlights box

- Safety of treatment options for SpA have been poorly addressed in international treatment recommendations;
- Similar to what observed in other conditions, the most common adverse events during NSAIDs therapy for SpA are gastrointestinal and cardiovascular;
- Amongst conventional DMARDs, leflunomide seems associated with a higher withdrawal rate; however, the global risk of DMARDs withdrawal due to adverse events is low;
- RCTs confirmed that apremilast is safe but extra care must be used in psychiatric patients because of the emerging risk of suicidal ideation and behaviour;
- Massive data demonstrated that TNF inhibitors are generally safe, in particular if adequate screening for identifying subjects at risk for TB and HBV reactivation is performed;
- Although less data are available, UST and SEC are generally considered safe.

Table 1. Number of adverse events (AE) and serious AE in selected clinical trials including patients with spondyloarthritis.

First author, year	Medication	Patients treated	All AEs (%)	Serious AEs (%)	Study duration	AEs occurring in ≥ 5% (listed by frequency)
Ankylosing spondylitis						
Dougados, 1999	NSAIDs	352	42.0	N.R.	52 w	Upper gastrointestinal AEs, nervous system disorders, skin disorders
Dougados, 1995	SSZ	179*	60.0	N.R.	6 m	Skin eruption
van der Heijde, 2005	IFX	202	82.2	3.5	24 w	URTI, infusion reaction, pharyingitis, ALT increase, headache, rhinitis, diarrhea, pain, AST increase, fatigue
Davis, 2003	ETN	138	N.R.	6.5	24 w	ISR, injection site bruising, URTI, headache, accidental injury, diarrhea, rash, rhinitis, abdominal pain, dizziness
van der Heijde, 2006	ADA	208	75.0	2.9	24 w	Nasopharyngitis, ISR, headache
Inman, 2008	GOL	278	79.9	4.7	24 w	Nasopharyngitis, URTI, fatigue, ISR, arthralgia, headache, ALT increase, cough, diarrhea, nausea, AST increase, pharyngolaryngeal pain
Landewe, 2014	CZP	111#	76.6	3.6	24 w	Nasopharyngits, ISR, URTI, headache, CK increase
Baeten, 2015	SEC	211	82.9	3.4	52 w	Nasopharyngitis, URTI, headache, diarrhea
Non-radiographic axial SpA						
Dougados, 2014	ETN	111	56.8	1.8	12 w	Infection
Sieper, 2013	ADA	95	57.9	3.2	12w	Infection
Sieper, 2015	GOL	97	41.2	1.0	16 w	Skin AEs
Psoriatic arthritis						
Kingsley, 2012	MTX	109	N.R.	N.R.	6 mo	Nausea and vomiting, URTI, abdominal pain, abnormal LFTs
Kaltwasser, 2004	LEF	96	63.5	13.5	24 w	Diarrhea, aggravation reaction, flu syndrome, increased ALT, headache, nausea, rash, join

						disorder, pruritus, gastrointestinal pain, tiredness, other skin disorders$
Fraser, 2005	CSA	38	N.R.	11.0	48 w	Nausea, headache, burning sensation, paraesthesia, muscle cramps, hypertrichosis
Kavanaugh, 2014	APR	168	61.3	5.4	24 w	Diarrhea, nausea, headache, increased ALT$
Antoni, 2005	IFX	150	67.0	9.0	24 w	URTI, infusion reaction, headache, increased ALT, pharyngitis, sinusitis$
Mease, 2005	ADA	151	N.R.	3.3	12 w	URTI, nasopharyngitis, ISR, headache, hypertension
Kavanaugh, 2009	GOL	146	68.0	2.0	24 w	Increased ALT, URTI, nasopharyngitis, headache
Mease, 2004	ETN	101	N.R.	4.0	24 w	ISR, URTI, IS ecchymosis, accidental injury, headache, sinusitis, UTI, rash
Mease, 2014	CZP	138	68.1	5.8	24 w	Nasophharyngitis, URTI, Diarrhea
McInnes, 2013	UST	205	40.0	2.0	16 w	-
McInnes, 2015	SEC	100	56.0	5.0	16 w	Nasopharyngitis

ADA, adalimumab; ALT, alanine aminotransferase; APR, apremilast; AST, aspartate aminotransferase; CSA, cyclosporin A; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; ISR, injection site reaction; LEF, leflunomide; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; SEC, secukinumab; SSZ, sulfasalazine; URTI, upper respiratory tract infection; UST, ustekinumab

* Classified according to European Spondylarthropathy Study Group (ESSG) criteria; # mixed population ankylosing spondylitis/non radiographic AxSpA

Table 2. Suggested monitoring strategies for drug treatment.

Drug	Pre-treatment evaluation	Major toxicities	Clinical monitoring	Laboratory monitoring
NSAIDs/ COXIBs	Clinical assessment, risk factors, CBC, LFTs, creatinine	Cardiovascular injury, renal injury, gastrointestinal ulceration	Dyspepsia, vomiting, black stool, abdominal pain and BP at each visit	CBC, LFTs and creatinine testing may be required
Glucocorticoids	Clinical assessment, risk factors, glycaemia, BP and bone densitometry in high-risk patients	Hypertension, diabetes	Polydipsia, weight gain, BP at each visit.	Glycaemia, urinalysis for glucose
Methotrexate	Clinical assessment, risk factors, CBC, LFTs, creatinine, serum albumin, hepatitis B and C serology, chest radiography. Consider pregnancy test, TST, IGRAs	Myelosuppression, hepatotoxicity, pulmonary fibrosis	Fever, dyspnea, asthenia, vomiting, symptoms of infection	CBC, LFTs and creatinine every 4 weeks for first 3 months (or after increasing the dose or resuming the therapy), then every 2-3 months; HBsAg every 3 months and HBV DNA every 6-12 months in chronic inactive HBV infection or a past HBV infection
Sulfasalazine	Clinical assessment, risk factors, CBC, LFTs, creatinine	Myelosuppression, hepatotoxicity	Fever, dyspnea, asthenia, vomiting, symptoms of infection	CBC, LFTs, creatinine every 4 weeks for first 3 months (or after increasing the dose or resuming the therapy), then every 2-3 months.
Leflunomide	Clinical assessment, risk factors, BP, CBC, LFTs, creatinine, hepatitis B and C serology. Consider pregnancy test	Myelosuppression, hepatotoxicity, hypertension, diarrhoea	BP at each visit, diarrhoea, symptoms of infection, dyspnea, asthenia,	CBC, LFTs, creatinine every 4 weeks for first 3 months (or after increasing the dose or resuming the therapy), then every 2-3 months; HBsAg every 3 months and HBV DNA every 6-12 months in chronic inactive HBV infection or a past HBV infection
Cyclosporine	Clinical assessment, risk factors, BP, CBC, creatinine, uric acid, LFTs	Renal injury, hypertension, anaemia	BP every week until dosage stable, then monthly	Creatinine every 4 weeks for first 3 months (or after increasing the dose or resuming the therapy), then every 2-3 months. CBC and LFTs may be required

Apremilast	Clinical assessment, risk factors, creatinine. Consider pregnancy test	Weight loss, diarrhoea, URTI, depression, suicidal ideation	Weight loss, symptoms of infection, depression	Creatinine every 3 months
TNF inhibitors	CBC, LFTs, creatinine, hepatitis B and C serology, chest radiography, IGRAs, TST	URTI, TB reactivation, HBV reactivation, infections, demyelinating disease	Symptoms of infection, dyspnea, symptoms of demyelinating disease	CBC, LFTs, creatinine every 2-3 months; IGRAs annually if TB exposure; HBsAg every 3 months and HBV DNA every 6-12 months in chronic inactive HBV infection or a past HBV infection
Ustekinumab	Clinical assessment, risk factors, CBC, LFTs, chest radiography, creatinine, hepatitis B and C serology, IGRAs, TST. Consider pregnancy test	URTI, TB reactivation, infections	Symptoms of infection, dyspnea	CBC, LFTs, creatinine every 2-3 months; IGRAs annually if TB exposure; HBsAg every 3 months and HBV DNA every 6-12 months in chronic inactive HBV infection or a past HBV infection
Secukinumab	Clinical assessment, risk factors, CBC, LFTs, chest radiography, creatinine, hepatitis B and C serology, IGRAs, TST, consider pregnancy test	URTI, TB reactivation, infections	Symptoms of infection, dyspnea	CBC, LFTs, creatinine every 2-3 months; IGRAs annually if TB exposure; HBsAg every 3 months and HBV DNA every 6-12 months in chronic inactive HBV infection or a past HBV infection

CBC: complete blood cell count; LFTs: liver function tests; BP: blood pressure; URTI: upper respiratory tract infection; IGRA: interferon gamma release assays; TST: tuberculin skin tests; TB: tuberculosis, HBV: hepatitis B virus.