

Review

Impact of Adverse Events Associated With Medications in the Treatment and Prevention of Rheumatoid Arthritis



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ABSTRACT

Purpose: Treatments for rheumatoid arthritis (RA) over the last few decades have transformed the future outlook of the disease. Although patients with clinically apparent RA have a number of therapeutic options, all are associated with the risk of adverse events (AEs). Such therapeutics, facilitated by the identification of novel biomarkers and environmental and genetic factors to predict RA, may allow early detection, prompt treatment, and prevention before the future development of clinically apparent disease. Before choosing such treatments to make informed decisions in this context, however, accurate quantification of benefits and harms of such treatments is vital for participants without symptoms. This review summarizes the AEs reported in trials in preclinical or very early RA, the frequency and risk of primary AEs of concern associated with disease-modifying antirheumatic drugs (conventional, biologic, and targeted), glucocorticoids, and analgesia in clinically apparent RA. Also summarized is the evidence to date to support the quantification of benefit and harms incorporating patient preferences.

Methods: This analysis is a narrative review in which individual searches were performed in PubMed and EMBASE for each drug and topic outlined in the review.

Findings: Current therapies in RA can result in a considerable burden of AEs (serious and nonserious) depending on the individual's baseline risk. The absolute risk of serious AEs to treatments reported in individuals at risk of RA, undifferentiated, or very early inflammatory arthritis trials was low; however, nonserious AEs were not consistently reported. If

such therapies prove effective at preventing the onset of RA in high-risk patients, incorporating patient preferences as well as robust quantification of benefits and harms to inform decisions is imperative. Patients' perceptions about treatment in this context may be risk averse or benefit driven. The risk of AEs that may not reverse after drug cessation, such as serious infection and malignancy, seem to be important AEs in such decision-making.

Implications: The impact of AEs in response to potentially preventative treatment is an important consideration for individuals at high risk of developing RA with minimal symptoms. Robust quantification of treatment effect given baseline risk versus the risks of developing all AEs (including those that may affect quality of life), while incorporating participants' views, will be necessary for future informed decision-making. (*Clin Ther.* 2019;41:1376–1396) © 2019 Published by Elsevier Inc.

Key Words: adverse events, biologics, disease-modifying antirheumatic drug, glucocorticoids, NSAIDs, rheumatoid arthritis.

INTRODUCTION

Treatment advances in rheumatology over the last 20 years and the identification of novel biomarkers for predicting the risk of developing rheumatoid arthritis

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(RA) hold promise that in the future, we might possibly be able to forecast and prevent RA at the preclinical phase. Patients with clinically apparent RA currently have a number of therapeutic options for short- and long-term disease modification and symptom relief. However, all medicines for RA are associated with adverse events (AEs), and therefore selecting the right therapy for the right patient is challenging as treatment decisions constantly require trade-offs between benefits and risks. In individuals at high risk of RA without symptoms, incorporating personal preferences for such a benefit/harm balance is especially important, is recognized as necessary by drug regulatory agencies,^{1,2} and is a vital step in the translation of research to treatment recommendations.^{3,4}

Adverse drug reactions have considerable economic as well as clinical costs, as they can often lead to hospital admissions, prolonged hospital stays, and emergency department visits, as well as affect patients' quality of life. A higher burden of AEs is also associated with a lower likelihood of remission in RA.⁵ In addition to treatment/disease related-immunosuppression, high disease activity, multimorbidity, and polypharmacy all likely contribute to the burden of AEs from conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologics in RA. In addition, in the majority of patients, treatments for RA are disease modifying and not curative; therefore, once started, patients are subject to lifelong medicines with a gradual rise of AE risk as they get older and accrue more comorbidities or use adjunct therapies for pain such as opioids and NSAIDs. For instance, the same medication with a high therapeutic index commenced at 30 years of age at the onset of disease is likely to develop a more narrow therapeutic index as the patient ages. Therefore, if proven to be an effective strategy, prevention of RA using such therapeutic agents may be a preferable alternative to avoid accrual of long-term sequelae as well as developing serious AEs (SAEs) (defined as episodes requiring hospitalization or resulting in death) over time. However, if such a strategy is to be effective, it must be based on informed decisions about the risks of administering such medicines.

The objective of the current review was to summarize the AEs of therapies used thus far in individuals at risk of very early RA trials. Because

such trials are often limited by short-term follow-up and may not represent real-world patients, we summarized the frequency of AEs of medicines used in clinically apparent RA. The preferences of individuals at risk for RA, quantification of benefit/harms incorporating patient preferences, and unmet needs in this area are also discussed.

MATERIALS AND METHODS

Literature searches were performed in PubMed and EMBASE for any of the following terms: "early rheumatoid arthritis," "pre-rheumatoid arthritis," "preclinical rheumatoid arthritis," "inflammatory arthralgia," "undifferentiated arthritis," and "polyarthritis." The goal was to identify clinical trials investigating preventing progression to RA in patients without a diagnosis of RA. Studies were included in this review if they reported safety data. We searched for relevant observational/registry studies, systematic reviews, randomized controlled trial (RCT) safety data, or summaries of product characteristics in clinically apparent RA (if required). Given the limitations of RCT data when reporting drug safety, recent large observational cohort studies were prioritized where available to derive the frequency estimates discussed in this review.

EARLY USE OF THERAPY IN SYSTEMIC AUTOIMMUNITY ASSOCIATED WITH RA, UNCLASSIFIED ARTHRITIS, OR VERY EARLY INFLAMMATORY ARTHRITIS

Studies to Date

Studies of patients with undifferentiated arthritis and individuals at risk of RA on the basis of laboratory abnormalities and symptoms, in which treatment has been studied to prevent progression to RA, have generally been short term: usually 12 months' follow-up, up to a maximum of 2 years. In those studies in which AEs were described, a variety of treatments have been analyzed, including a single injection of glucocorticoids (GCs), methotrexate (MTX), and combinations of csDMARDs and biologics alone or in combination with a csDMARD (Table I).⁶⁻¹⁷ In terms of efficacy for preventing RA, studies thus far have found that RA onset may be delayed but not prevented. Only 2 studies reported statistically significant benefit: the STIVEA (Steroids In Very Early Arthritis) trial found that 3 GC intramuscular injections over 3 weeks reduced the

Table I. Summary of treatments and adverse events (AEs) reported in key trials of patients with unclassified arthritis, very early rheumatoid arthritis (RA), and systemic autoimmunity.

Author/Year (Trial Name)	Treatment Intervention	Type of Disease	No. of Patients in Trial (No. in Intervention Arm)	AEs/No. of Patients	AE Type Reported in Intervention Arm			Outcome
					GI	Infection	Other	
IM glucocorticoids								
Machold et al, 2010 (SAVE trial) ⁶	Single IM 120-mg methylprednisolone	Very early arthritis (symptom duration <16 wk)	383 (198)	22 SAEs in 20 patients (12 patients in treatment arm; 6 taking placebo)	—	—	1 SAE attributed to the treatment drug: worsening of pustulous psoriasis	Clinical remission at 12 and 52 wk. No difference seen between 2 groups
Verstappen et al, 2010 (STIVEA) ⁷	Three injections of 80-mg IM methylprednisolone acetate 1 wk apart	Very early arthritis (4–10 wk duration)	268 (133)	36 AEs in 26 patients (10 associated with treatment; 7 in the glucocorticoid group 3/3 on placebo)	1 SAE due to severe abdominal pain	—	2 severe reactions, including anaphylaxis	Need to start DMARDs at 6 mo. Placebo group significantly more likely to start DMARDs at 6 mo
csDMARDs								
van Dongen et al, 2007 (PROMPT study) ¹⁰	MTX 15 mg/wk for up to 12 mo	Unclassified arthritis	110 (55)	26/55 (47% of MTX patients developed an AE [5 SAEs] vs 33% taking placebo [4 SAEs])	1 event requiring discontinuation of MTX	—	1 event of erythema annulare centrifugum Pancreatitis	Diagnosis at 30 months; 40% of the MTX group had progressed to RA compared with 53% in the placebo group. MTX group RA diagnosis was postponed but not prevented
Biologics								
Saleem et al, ¹⁴ 2008	Infliximab (4 doses over 14 wk)	Unclassified arthritis	17 (10)	2 SAEs, both in the infliximab group	—	1 patient with recurrent chest infections	1 event of drug-induced antineutrophil cytoplasmic antibody-positive vasculitis	Remission at week 26; 1/7 in the placebo group and 2/10 in the infliximab group were in remission at week 26
Emery et al, 2010 (ADJUST trial) ⁸	Abatacept 10 mg/kg for 6 mo	Unclassified arthritis	56 (28)	18/24 (64%) vs 20/24 (71%) patients experienced AEs in the abatacept vs placebo arm, including follow-up period up to 56 days after the last dose. 1	—	10 abatacept-treated patients (most common nasopharyngitis, urinary tract infections, and gastroenteritis)	1 SAE of a basal cell carcinoma 1 infusion reaction	Abatacept delayed progression to RA, but the primary outcome (development of RA at 1 y) was not met; 46% of the abatacept group and 67% of

Table I. (Continued)

Author/Year (Trial Name)	Treatment Intervention	Type of Disease	No. of Patients in Trial (No. in Intervention Arm)	AEs/No. of Patients	AE Type Reported in Intervention Arm			Outcome
					GI	Infection	Other	
				SAE reported in each arm				the placebo group in remission at 1 y. No statistically significant difference between groups
Nam et al, 2014 (EMPIRE trial) ¹⁷	Etanercept 50 mg + 10 –20 mg MTX/wk	Very early inflammatory arthritis (<3 mo)	110 (55)	53/55 (96% of patients on etanercept + MTX developed AEs vs 100% of MTX + placebo patients.	Higher incidence of SAEs in the etanercept + MTX group: 16.4/100 pyrs compared with 3.7/100 pyrs in the MTX + placebo group	1 GI SAE- believed to be probably not related to etanercept + MTX	195 infectious episodes recorded in total: 90 in 43 patients in the MTX + etanercept group (2 SAEs) and 105 in 37 patients in the MTX + placebo group (0 SAEs)	No tender or swollen joints at week 52; 33% in the etanercept + MTX group and 28% in the MTX + placebo group had no tender or swollen joints. No significant difference was observed
Gerlag et al, 2019 (PRAIRI study) ⁹	Single rituximab 1-g dose	Participants both anti-CCP and rheumatoid factor positive without arthritis	82 (41)	SAE rate significantly higher in the rituximab group vs placebo (13/41 vs 3/40). However, all SAEs believed not to be related to study drug	–	–	Mild infusion reactions	Time to development of clinical arthritis. Rituximab delayed treatment for 12 mo

ADJUST = Abatacept Study to Determine the Effectiveness in Preventing the Development of RA in Patients With Undifferentiated Inflammatory Arthritis; CCP = citrullinated peptide; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; EMPIRE = Etanercept and Methotrexate in Patients to Induce Remission in Early Arthritis; GI = gastrointestinal; IM = intramuscular; mo = months; MTX = methotrexate; PRAIRI = Prevention of RA by Rituximab; PL = placebo; PROMPT = The PROBable rheumatoid arthritis: Methotrexate versus Placebo Treatment; pyrs = patient years; SAEs = serious adverse events; SAVE = Stop Arthritis Very Early; STIVEA = Steroids In Very Early Arthritis.

need to start DMARDs at 6 months. In the Prevention of RA by Rituximab (PRAIRI) trial, a single rituximab injection delayed the RA onset by 12 months.

AEs in individuals at risk of RA/Studies

Several studies have reported only on SAEs rather than all AEs, resulting in a small number of events with a similar frequency between the treated and untreated groups.^{6,7,12} Biologics have been the most frequently studied; often in these studies, the biologics group have reported more AEs. When reporting AEs, often the primary focus was on the risk of infection, and clear signals of increased risk of infection have not been seen. The most recently published PRAIRI study, which explored the effects of a single infusion of rituximab 1 g compared with placebo administered to individuals at risk of developing RA but without inflammatory arthritis, reported significantly higher SAEs in the rituximab group, but reassuringly none was considered to be related to treatment.⁹ These included events such as myocardial infarctions, hospitalization for chronic obstructive pulmonary disease exacerbations, and elective surgeries for joint replacements; there were no reported serious infections. In the ADJUST (Abatacept Study to Determine the Effectiveness in Preventing the Development of RA in Patients With Undifferentiated Inflammatory Arthritis) trial comparing abatacept with placebo, there were numerically but not statistically fewer AEs in the abatacept group compared with the placebo group (64% vs 71%) and only 1 SAE in each group. There were discontinuations due to infections, but this occurred at a similar frequency in both groups.⁸ In the EMPIRE (Etanercept and Methotrexate in Patients to Induce Remission in Early Arthritis) study, patients were randomized to receive MTX + etanercept or MTX + placebo; the etanercept group had more SAEs, and 2 were possibly related to the study medication (one was metastatic breast cancer, and the other was an upper respiratory tract infection). In terms of infections, there were a large number of infections reported; 2 were severe, and both were for patients in the etanercept group. However, RCTs in general may recruit patients with fewer comorbidities and less polypharmacy compared with real-world patients; participant numbers in the majority of such biologics trials are low, however, and therefore may

underrepresent rare AEs and make safety estimates difficult to interpret.

In studies of intramuscular GCs, only 2 reported AEs. The STIVEA trial assessed whether treating patients with very early inflammatory arthritis with a 3-week course of intramuscular GC may prevent evolution to RA. It reported that GC injections were associated with severe allergic reactions to the injection itself, cramps and soreness in the legs, mood swings, and increased alanine transaminase levels that were probably or possibly related to treatment.⁷ The SAVE (Stop Arthritis Very Early) trial assessed a single intramuscular GC injection in very early arthritis and reported 22 SAEs; however, only 1 worsening of pustulosis psoriasis was attributed to the treatment.⁶ In studies of MTX, gastrointestinal (GI) symptoms were reported by 20%–50% of patients in studies of MTX either alone or in combination with other csDMARDs/biologics, and they were the most frequently reported AEs with such drugs.^{10–12} Studies of combination treatments compared with single treatments reported more AEs in those treated with the combinations.^{11,18}

Several more RA prevention trials are currently in the recruitment stage in the United States and across Europe. However, compared with the few previous studies that administered a single dose or a short course of therapy to at-risk patients without clinical features of RA (Table I), participants are exposed to the interventional drug for longer. The aim of the Stop-RA (Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis) trial is to evaluate if hydroxychloroquine is safe and effective for the prevention of future onset of RA in participants who have elevations of anti-citrullinated peptide (CCP) antibodies ≥ 2 times the normal value but without joint symptoms. Participants will be randomized to receive 200–400 mg of hydroxychloroquine or placebo, to be taken daily for 12 months.¹⁹ The APIPPRA (Arthritis Prevention in the Pre-Clinical Phase of RA with Abatacept) trial aims to assess if the onset of RA in an at-risk group can be prevented or delayed by weekly injections of abatacept over 12 months.²⁰ At-risk participants are those with arthralgia and who are positive for both rheumatoid factor and anti-CCP or anti-CCP levels ≥ 3 times the upper limit of normal. In a similar population to APIPPRA, the STAPRA (Statins for the Prevention of

Rheumatoid Arthritis) trial is currently evaluating the effect of atorvastatin versus placebo over 3 years.²¹ Apart from addressing their primary outcomes, a longer treatment exposure will allow more useful comparisons of safety outcomes vs existing data of the same treatments in patients with clinically apparent RA (as described earlier) and aid toward quantification of absolute risk of AEs in this unique subset of individuals for informed decision-making.

AEs of Therapies in Clinically Apparent RA

The trials reported in the above section, are limited by short-term follow up and fewer patient numbers, therefore provide limited data on safety outcomes. Thus, the following sections discuss the most common AEs that are expected with drugs normally used to treat clinically apparent RA that may be used in prevention.

CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC AGENTS GI AEs

The frequency of the main AEs of csDMARDs is summarized in [Table II](#). MTX is widely regarded as the anchor drug in RA; hydroxychloroquine, leflunomide, and sulfasalazine are also effective and are commonly used as monotherapy or in combination with MTX. The most frequently reported AEs across all csDMARDs are GI symptoms,^{22–26} with up to a 50% increased risk of nausea and vomiting in those treated with MTX compared with placebo (rate ratio [RR], 1.47; 95% CI, 1.27–1.70).²³ In long-term observational studies, ~30% of withdrawals of MTX are due to GI symptoms (again the most common AE reported^{27,28}) ([Table I](#)). Similar relative risks of GI reports are seen in those treated with leflunomide compared with placebo (RR, 1.6; 95% CI, 1.18–2.2).²⁴ Of hydroxychloroquine users, 10% have GI symptoms severe enough to result in a loss of appetite.²⁹ In patients undergoing combination or triple therapy, risk attribution of GI side effects is challenging, whereas 1 study assessing triple therapy concluded that AEs were mainly attributed to sulfasalazine.³⁰ Studies have shown that GI symptoms significantly impair quality of life in patients with RA, with dyspepsia and upper GI pain having the most impact on quality of life.³¹

Abnormal Liver Function Test Results

Another frequent AE associated with csDMARDs is hepatotoxicity. MTX and leflunomide have similar toxicity profiles in terms of hepatotoxicity,^{23,24} and long-term studies of MTX found that between 12% and 18.5% reported abnormal liver function test results.^{27,28} Duration of MTX therapy and cumulative MTX dose seem to increase the likelihood of this AE.^{32,33} Although liver toxicity associated with sulfasalazine has been studied less extensively, it appears less frequently in studies (between 1% and 2.4%) ([Table II](#)).³⁴

Other Events

MTX use has been associated with a 67% increased risk of leukopenia and a 2-fold increased risk of thrombopenia compared with placebo.²³ However, the frequency of hematologic events is low, with only 2%–4% of MTX users reporting disturbances. A similar frequency of events has been described with sulfasalazine, with reports of <3% of patients reporting disturbances.²⁶ Other commonly described AEs are mucocutaneous, such as mouth ulcers and rashes.^{23,35} Frequencies of hematologic disturbances, infections, and rarer AEs such as hydroxychloroquine retinopathy are summarized in [Table II](#).

Biologics and Targeted Synthetic DMARDs in RA

Although biologic DMARDs and targeted synthetic DMARDs (tsDMARDs) have been found to be highly effective in clinically apparent RA, trials thus far show similar efficacy between such drugs, especially when used in combination with MTX. There are, however, differences in AE profiles between the classes of these drugs that need to be considered when risk-stratifying individual patients for such treatments. The risk of AEs from the current literature is summarized for biologics and for tsDMARDs in [Tables III and IV](#), respectively.

Biologics

Infection Risk

The potential risk of infection is one of the most important considerations before starting biologic treatments in clinically apparent RA. Biologics are known to be associated with a higher risk of serious infection compared with csDMARDs, with a time-varying risk highest in the first 6–12 months of

Table II. Adverse events (AEs) associated with conventional synthetic disease-modifying antirheumatic agents in clinically apparent rheumatoid arthritis.

Type of Study	Study Details	Total AEs	Serious AEs	Gastrointestinal Symptoms	Hepatotoxicity	Hematologic Disturbance	Infections	Comments/Other Frequent or Serious AEs
MTX								
Salliot et al, ²⁷ 2009	Systematic review: 88 studies (meta-analyses, prospective cohorts, and case-control studies) with >2 yrs follow-up. 3463 patients	2524	Not reported	30.8%	18.5%	—	Serious infections, 8.3%	Long-term MTX not associated with increased risk of infection in this review
Mazaud et al, ²³ 2017	Systematic review: 68 studies of MTX vs placebo that reported AEs 6938 patients	—	264/3188	Abdominal pain, 13.3% Nausea/vomiting, 26.4% Diarrhea, 11.4%	Elevated ALT, 11.3% Elevated AST, 4.1%	Leukopenia, 4.2% Thrombopenia, 2%	Infections, 50%	Mucosal ulcerations, 9.7%
Sulfasalazine								
Suarez-Almazor et al, ³⁶ 1998	Systematic review: 6 trials of sulfasalazine vs placebo 468 patients	—	—	9.7%	2.4%	1.9%	—	% refer to withdrawals and dropouts due to AEs
Amos et al, ³⁷ 1986	Cohort study: Medical records of 774 patients who were prescribed sulfasalazine for ≥1 y	205	—	19%	1%	Leukopenia, 1%	—	% refer to withdrawals and dropouts due to AEs
Hydroxychloroquine								
Fries et al, ³⁸ 1993	Observational study: postmarketing surveillance (ARAMIS data bank); 1014 years at risk	639	—	Nausea, 19/1000 pyrs Vomiting, 2/1000 pyrs Upper abdominal pain, 16/1000 pyrs	Liver problems, 1/1000 pyrs	—	—	Hydroxychloroquine had lowest toxicity compared with gold, penicillamine, MTX, azathioprine, auranofin, and prednisone
Van Jaarsveld et al, ³⁹ 2000	RCT: Patients randomized to receive hydroxychloroquine, gold, MTX, or NSAIDs 120 patients randomized to receive hydroxychloroquine and followed up for 2 y	91	—	Nausea, vomiting, dyspepsia, abdominal pain, indigestion, 21 events Diarrhea, 5 events	Elevated transaminase levels or GGT, 1 event	Anemia, 2 events Eosinophilia, 1 event	Fever, infections, 19 events	—
Jorge, ⁴⁰ 2018	Systematic review	—	—	—	—	—	—	Prevalence of hydroxychloroquine retinopathy between 1.5% and 8% depending on the sensitivity of the screening method High-dose (>5 mg/

Table II. (Continued)

Type of Study	Study Details	Total AEs	Serious AEs	Gastrointestinal Symptoms	Hepatotoxicity	Hematologic Disturbance	Infections	Comments/Other Frequent or Serious AEs
Leflunomide Osiri et al. ²⁴ 2003	Systematic review: 6 trials of LEF vs placebo with follow-up of ≥6 mo 2586 patients	—	—	18%–33.5%	2.7%–14.8%	—	4.5%–56.6%	kg) and long-term (>5 y) use believed to be risk factors Hypertension, 11%
Schultz et al. ⁴¹ 2017	Cohort data: 1671 patients with LEF use enrolled on prospective registry	249	—	Diarrhea, 8%	Liver dysfunction, 4%	—	Serious infection, 6%	Hypertension, 2%

ALT = alanine transaminase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; LEF = leflunomide; MTX = methotrexate; yrs = patient years; ARAMIS = The American Rheumatism Association Medical Information System.

treatment.^{42,43} A large meta-analysis using clinical trial data reported a 31% higher serious infection risk with standard-dose biologic-treated patients with RA compared with csDMARD-treated patients (odds ratio [OR], 1.31; 95% CI, 1.09–1.58).⁴⁴ This finding translates to an absolute increase in number of serious infections associated with biologics as 6 per 1000 patients treated per year for standard-dose biologics. The most common types of serious infections in biologic-treated patients with RA are respiratory (22 per 1000 patient-years), skin and soft tissue (11 per 1000 patient-years), genitourinary (6.2 per 1000 patient-years) infections.⁴⁵ In particular, tumor necrosis factor (TNF) inhibitors, especially monoclonal antibodies, are known to increase the risk of reactivation of latent tuberculosis and new events, with a differential risk between drugs.⁴⁶ For other opportunistic infections, the absolute risk reassuringly is low at just above 1 per 1000 patient-years.⁴⁷ However, the majority of evidence thus far represents population-level risk, and accurate individual risk stratification of serious infection based on patient characteristics is challenging.⁴⁸ Thirty-day mortality after a serious infection remains high at 10.4% (95% CI, 9.2–11.6), with sepsis/bacteremia associated with the highest mortality at 45% (95% CI, 33–61).⁴⁵

Drug Hypersensitivity Reactions

Drug hypersensitivity reactions ranging from injection site reactions to severe infusion reactions have been reported in biologic-treated patients. Infusion reactions can vary from anaphylaxis to delayed hypersensitivity reactions and serum sickness type reactions, often secondary to immunogenicity of the drug.⁴⁹ Patients taking rituximab, infliximab, abatacept, and tocilizumab intravenous infusions have a statistically significant higher risk of hypersensitivity reactions compared with injectable TNF inhibitor drugs; however, the absolute risk of hypersensitivity reactions remains low at <1%.⁵⁰ However, apart from mitigating risk by taking concomitant csDMARDs such as MTX, there are no predictors before treatment to determine which patients may develop these events in the future.

Malignancies

TNF has pleotropic effects in malignancy progression, with potential paradoxical cancer-

Table III. Adverse events associated with biologics in clinically apparent rheumatoid arthritis (RA).

Variable	Type of Study	No. of Patients	Serious Infection	Malignancy	Infusion Reaction	Others	Comments
TNF inhibitors							
Rutherford et al, ⁴⁵ 2018	Observational	19,282 (46,771 years FU) Etanercept, 8630 Adalimumab, 7818 Infliximab, 4908 Certolizumab, 1446	Incidence/100 pyrs (95% CI) Etanercept, 5.56 (5.20–5.95) Adalimumab, 5.42 (5.04–5.84) Infliximab, 5.35 (4.89–5.85) Certolizumab, 3.80 (2.97–4.95)	–	–	–	Most common type of infections were respiratory tract infections followed by skin and soft tissue infections
Dixon et al, ⁴⁶ 2010	Observational	10,712 Etanercept, 3913 Infliximab, 3295 Adalimumab, 3504	Rate of TB (events) Adalimumab, 144/100,000 person-years Infliximab, 136/100,000 person-years Etanercept, 39/100,000 person-years	–	–	–	Median time to event was lowest for infliximab (5.5 mo) compared with etanercept (13.4 mo) and adalimumab (18.5 mo) 62% cases were extrapulmonary, of which 11 were disseminated Patients of non-white ethnicity had a 6-fold increase risk of TB compared with white patients treated with TNF inhibitors
Rutherford et al, ⁴⁷ 2018	Observational	85,331 pyrs FU Total = 19,282 with 106,347 years FU	No. of OI, 114 OI incidence rate (95% CI) unadjusted: 134 (111–161)/100,000 pyrs	–	–	–	Most common OI with TNF inhibitor therapy: HZ (54/114) PJP (15/114) Legionella (11/114)
Mercer et al, ⁵⁵ 2017	Observational	11,931 (TNF inhibitors)	–	Lymphomas in TNF inhibitor group: 88 (95% CI, 70–190)/100,000 person-years	–	–	No differences in the risk of lymphoma for TNF inhibitor vs biologic-naive group No risk differences were observed for individual TNF inhibitors
Mercer et al, ⁶¹ 2016	Observational	3363 (biologic-naive)	–	Lymphomas in biologic-naive group: 154 (95% CI, 104–220)/100,000 person-years	–	–	IRR vs biologics-naive patients, 1.1 (95% CI, 0.8–1.6)
Mercer et al, ⁵⁴ 2015	Observational	130,315 (579,983 person-years) 11,767	–	SIR for melanoma, 1.2 (95% CI, 0.99–1.6)	–	–	No difference in risk of solid cancer for TNF inhibitors compared with csDMARD group: HR, 0.83 (95% CI, 0.64–1.07) No difference in the relative

Table III. (Continued)

Variable	Type of Study	No. of Patients	Serious Infection	Malignancy	Infusion Reaction	Others	Comments
Yun et al, ⁵⁰ 2017	Observational	48,293 (TNF inhibitor) 725,591 (total)	—	Solid cancers, 81 (95% CI, 74–89)/10,000 pyrs	—	Hypersensitivity reactions: Infliximab, 22.9% Other TNF inhibitor, 39.7%	risk of cancer for any individual TNF inhibitor
Jani et al, ⁵⁹ 2017	Observational	12,937 (TNF inhibitor)	—	—	—	LLE incidence rate, 10 (95% CI, 8–13)/10,000 pyrs	
Dreyer et al, ⁶² 2016	Observational	3673 (biologic-naïve) 5647 (TNF inhibitor) 11,974 (TNF inhibitor-naïve)	—	—	—	VLE incidence rate, 15 (95% CI, 12–19)/10,000 pyrs SIR of MS in TNF inhibitor—treated patients, 0.67 (95% CI, 0.17–2.66) during 53,723 pyrs SIR of MS in TNF inhibitor-naïve patients, 0.64 (95% CI, 0.16–2.54) during 59,804 pyrs	
Abatacept Grøn et al, ⁶³ 2019	Observational	2725 (abatacept) 8987 (total)	Adjusted IR (95% CI)/ 100 pyrs 0–12 mo: Denmark, 7.1 (5.1–9.9) Sweden, 6.0 (4.8–7.5) 0–24 mo: Denmark, 6.1 (4.4–8.3) Sweden, 5.6 (4.6–6.7)	—	—	—	
Núßlen et al, ⁶⁴ 2014	Observational	1138	—	—	—	Serious cardiac disorder, 0.44% Vascular disorders, 0.26% (stroke, TIA, DVT) Diverticular perforation, 0.1% Pulmonary disorders, 0.6%	1.8% of patients discontinued drug due to SAE No cases of active TB reported
Montastruc et al, ⁶⁵ 2018	Observational	4328 (abatacept) 59,860 (other bDMARDs)	—	4.76/100 person-years (including NMSC) vs 3.41/100 person-years for other bDMARDs	—	—	Breast cancer, 0.74/100 person-years Lung cancer, 0.24/100 person-years Lymphoma, 0.24/100 person-years

(continued on next page)

Table III. (Continued)

Variable	Type of Study	No. of Patients	Serious Infection	Malignancy	Infusion Reaction	Others	Comments
Salmon et al, ⁶⁶ 2018	Observational	2293 pyrs (abatacept) Total = 12,663 pyrs	—	—	0.6/100 pyrs (1.5% of patients)	—	Melanoma, 0.09/100 person-years NMSC, 2.12/100 person-years Serious infusion reactions
Tocilizumab Grøn et al, ⁶³ 2019	Observational	2899 (tocilizumab) 8987 (total)	Adjusted IR (95% CI)/ 100 pyrs 0–12 mo: Denmark, 6.1 (4.6 –8.1) Sweden, 4.7 (3.7 –6.1) 0–24 mo: Denmark, 5.2 (4.1 –6.7) Sweden, 4.3 (3.4 –5.3)	—	—	—	
Souto et al, ⁶⁷ 2015	Systematic review and meta- analysis	6 RCTs of tocilizumab (20 articles)	—	—	—	Risk of hypercholesterolemia compared with placebo: OR, 4.64 (95% CI, 2.71–7.95) [$P < 0.0001$] with heterogeneity ($I^2 = 43.4%$)	Patients with RA treated with tocilizumab were more likely to have high LDL cholesterol by the end of the trial than placebo in 4 studies ($P < 0.001$) and more HDL cholesterol than placebo in 3 studies ($P < 0.20$)
Strangfeld et al, ⁶⁸ 2017	Observational	1765 (13,600 total)	—	—	—	11/1765 cases of lower intestinal perforation 5 times higher incidence rate than in patients treated with csDMARDs (IRR, 5.1; 95% CI 2.2 –11.8)	Incidence rate of lower intestinal perforation was also higher compared with other bDMARDs
Burmester et al, ⁶⁹ 2017	RCT	1262	6.65/100 pyrs (SC) 3.92/100 pyrs (IV)	—	(0.23%) 3 hypersensitivity reactions	Neutropenia Grade (SC %, IV %) Grade 1, 21.5%; 19.9% Grade 2, 17.1%; 11.8% Grade 3, 5.4%; 6.7% Grade 4, 0.6%; 0%	0 cases of anaphylaxis, (0.23%) 3 patients had GI perforation within 24 h of injection/ infusion

Table III. (Continued)

Variable	Type of Study	No. of Patients	Serious Infection	Malignancy	Infusion Reaction	Others	Comments
Rituximab							
Grøn et al, ⁶³ 2019	Observational	3363 (rituximab) 8987 (total)	Adjusted IR (95% CI)/ 100 pyrs 0–12 mo: Denmark, 8.1 (5.9 –11.0) Sweden, 6.5 (5.3 –7.7) 0–24 mo: Denmark, 7.5 (5.8 –9.7) Sweden, 5.8 (5.0 –6.8)	–	–	–	
Rutherford et al, ⁴⁷ 2018	Observational	17,154 pyrs FU Total = 19,282 with 106,347 years FU	No. of OI, 25 OI incidence rate (95% CI) unadjusted: 146 (91–217)/ 100,000 pyrs	–	–	–	Most frequently observed OI in rituximab: PJP (9/25) HZ (7/25)
Slimani et al, ⁷⁰ 2011	Observational	186 346 pyrs exposure (12.9% had history of malignancy)	–	1.45/100 pyrs (95% CI, 0.19–2.70) 2.7% (5 cancers detected, 4 new and 1 re- occurrence)	–	–	New malignancies: prostate, breast, colon, cervical Re-occurrence, breast No hematologic malignancies and 6 lymphomas in remission, remained so on FU

bDMARDs = biologic disease-modifying antirheumatic drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DVT = deep vein thrombosis; FU = follow-up; HDL = high-density lipoprotein; HR = hazard ratio; HZ = herpes zoster; IR = incidence ratio; IRR = incidence rate ratio; IV = intravenous; LDL = low-density lipoprotein; LLE = lupus-like event; MS = multiple sclerosis; NMSC = non-melanoma skin cancer; OI = opportunistic infections; OR = odds ratio; PJP = *Pneumocystis jirovecii* pneumonia; pyrs = patient-years; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SIR = standardized incidence ratio; TB = tuberculosis; TIA = transient ischemic attack; TNF = tumor necrosis factor; VLE = vasculitis-like event.

promoting and -inhibiting actions.⁵¹ Early in the development of biologics such as TNF inhibitors, there was a concern regarding increased malignancy risk. The initial meta-analyses based on clinical trials fueled concerns regarding an almost 4-fold increase in solid cancer risk in infliximab- and adalimumab-treated patients compared with those receiving placebo.⁵² RA as a disease itself is known to be associated with an established increased risk of lymphoma compared with the general population,⁵³ and because biologics are administered to patients with high RA disease activity, confounding by indication is a clear concern in such studies. More recent observational and registry studies with medium-term (5-year) follow-up data have provided reassurance that there is no evidence that biologics such as TNF inhibitors increase the risk of lymphoma or solid cancer over the background risk in individuals with clinically apparent RA.^{54–56} Similarly, the risk of non-melanoma skin cancers is higher in patients with RA, but TNF inhibitors do not seem to exacerbate the risk of basal cell carcinomas and squamous cell carcinomas.⁵⁷ Overall risk of patients with RA starting a TNF inhibitor such as abatacept, tocilizumab, or rituximab does not significantly differ from csDMARD-treated patients with RA; however, due to the rarity of such events, altered risks for longer latency malignancy or specific subtypes of cancers cannot be excluded.⁵⁸

Rare AEs

Lupus-like events and vasculitis-like events have been reported in patients taking TNF inhibitors. Although the absolute risk of these events is low (10 per 10,000 patient-years and 15 per 10,000 patient-years, respectively), patients with high disease activity and high disease burden were associated with having an increased risk of such events.⁵⁹ Other rare AEs include hematologic abnormalities, exacerbation of congestive heart failure and noninfectious serious respiratory AEs (SRAEs). Biologic therapies may lead to such SRAEs through a number of mechanisms, including idiosyncratic adverse drug reactions (eg, acute hypersensitivity pneumonitis), acceleration of a pre-existing pathologic process such as RA-Interstitial lung disease and conversion of a pre-existing disease process into a more injurious phenotype (eg, precipitation of diffuse alveolar damage on a

background of usual interstitial pneumonia).⁶⁰ Effective treatment to the right individuals at risk of RA to prevent the onset of disease would therefore avert morbidity due to both RA-associated comorbidity as well as SRAEs related to medication.

POLYPHARMACY IN EARLY OR UNCONTROLLED RA DISEASE

Glucocorticoids

GCs are effective at reducing inflammation in RA and are widely used in up to 50% of patients with incident RA in the United Kingdom.⁷³ In the United States, it has been estimated that two thirds of patients with RA are prescribed GCs at some point during their disease course.⁷⁴ The European League Against Rheumatism recommends that short-term GCs be used as a bridging therapy with starting or changing DMARDs because combining GCs with csDMARDs or biologics improves efficacy of these drugs in established disease.⁷⁵ In early RA, GCs are recommended as an adjunct to csDMARDs if necessary.⁷⁶

SAEs of GCs have been more widely studied, with cardiovascular disease and infections being the most frequently reported in studies.^{77,78} Infections are frequently experienced in GC-treated patients, and this risk seems to be independent of dose, duration, and recency. It has been shown that current GC dose and doses within the previous 6 months confer the greatest risk of infection, but there was still a small increased risk from cumulative GC doses up to 2.5 years before the infection. High doses confer the greatest risk; for example, current users at 30 mg for past 3 months had an OR of 4.82 (95% CI, 3.12–9.29) compared with nonusers. Similarly, lower doses were associated with a lower infection risk: current users of 5 mg for the past 7 days had an OR of 1.03 (95% CI, 1.02–1.11) compared with nonusers.^{79,80} Another study of patients with RA over a 7-year follow-up found no increased risk of infections comparing GC and non-GC users, in which the mean dose for GC users was 3.1 mg/d.⁸¹ Long-term GCs are associated with a considerable burden of AEs, including GI, psychological/behavioural, metabolic, dermatologic, musculoskeletal, and ophthalmologic manifestations.⁸² Interestingly, the AEs discussed the most by patients taking GCs and likely of most concern are nonserious such as weight gain and insomnia, likely due to their potential impact on quality of life.^{83,84} Preventing or delaying the onset

of RA, thereby reducing the cumulative exposure to GCs, would help reduce both serious AEs and important AEs affecting patients' well-being.

USE OF CONCOMITANT ANALGESIA

Opioids

Chronic pain in RA may be due to a number of reasons, including uncontrolled inflammation, structural damage through erosive disease, or secondary osteoarthritis. Opioids are regularly administered in musculoskeletal conditions for chronic pain, with 40% of patients with RA in a US study using prescription opioids daily.⁸⁵ There has been a sharp increase in prescription opioid use for nonmalignant pain in the United States, Canada, and several European countries,^{86–88} with concerns about subsequent chronic use, dependency, and overdose. In patients taking opioids, serious harms have been well documented, including respiratory depression, GI-related harms, falls, fractures, motor vehicle accidents, endocrinologic harms, infections, cardiovascular events, and cognitive and psychological harms.⁸⁹

One emerging concern with opioids is the risk of infection.⁹⁰ Risk of serious infection has been shown to be higher with use of long-acting opioids, immunosuppressive opioids (codeine, morphine, and transdermal fentanyl), and those with a daily morphine milligram-equivalent dose of ≥ 60 mg/d. Opioids have also been found to be an independent risk factor of invasive pneumococcal disease, including associated bacteremia, meningitis, and invasive pneumonia.⁹¹ Therefore, patients with clinically apparent RA receiving multiple treatments for their disease and chronic pain may be at particularly high danger of harms such as infection risk.

NSAIDs

NSAID use is ubiquitous in RA, especially during early or uncontrolled disease primarily due to their anti-inflammatory and analgesic properties. They are also associated with a spectrum of harms, including GI (eg, dyspepsia, esophagitis/gastritis, peptic ulcers), renal failure, vascular outcomes (eg, myocardial infarctions, heart failure, stroke), hepatic toxicity (eg, abnormal liver function test results), and exacerbation of asthma/dyspnea.⁹² Of these, some have a differential risk within class as seen in one of

the largest meta-analyses from RCTs. Major vascular events, including vascular deaths, are increased by more than one third using a coxib (rate ratio [RR], 1.37; 95% CI, 1.14–1.66) or diclofenac (RR, 1.41; 95% CI, 1.12–1.78). However, all NSAIDs increase upper GI complications and double the risk of heart failure. The highest risk of GI complications is in naproxen-treated patients (RR, 4.22; 95% CI, 2.71–6.56).⁹³

QUANTIFICATION OF BENEFIT AND HARMS IN INDIVIDUALS AT RISK OF DEVELOPING RA

Patient Preferences

Even if the onset of RA could be delayed or prevented completely, the decision regarding medicines with even the potential of SAEs is challenging and multifactorial, especially for individuals with minimal symptoms. Individual factors such as the perceived likelihood of developing the disease in the future and experience of the disease are important,⁹⁴ as are treatment characteristics and severity of the diagnosis in influencing the individual's willingness to undergo preventative therapies. Even in patients diagnosed with RA, in whom antirheumatic treatment benefits are high to prevent long-term disability, adherence to antirheumatic medications can be as low as 23%–41%.⁹⁵ Individuals who are asymptomatic or with minimal symptoms face further uncertainties around accurate estimates regarding the risk of developing RA and quantifying the benefit/harm balance of therapies for preventing this condition.

To assess what factors were of highest importance when considering a therapeutic intervention in this context, a binary choice experiment (stated choice survey) was conducted in asymptomatic first-degree relatives of patients with RA (deemed to be high risk).⁹⁶ Participants chose to take the proposed antirheumatic medications more often as the hypothetical risk of RA increased. Only 7% of participants would choose treatment if the risk of developing RA was 1%; however, this increased to 30% if the risk was set at 20%. A lower probability of SAE risk $\leq 10\%$ and reduction of RA risk development $\geq 20\%$ were both significantly associated with the odds of accepting preventative therapies. The study suggested that preventative efficacy was deemed at least as important as risk of SAEs by participants.⁹⁶ However, in a discrete choice

Table IV. Adverse events associated with targeted synthetic disease-modifying antirheumatic drug in clinically apparent rheumatoid arthritis (RA).

Variable	Type of Study	No. of Patients	Serious Infection	Malignancy	Others	Comments
Baricitinib						
Kunwar et al, ⁷¹ 2018	Systematic review and meta- analysis	2485 (479 baricitinib 2 mg; 967 baricitinib 4 mg; 1039 placebo)	Baricitinib 2 mg vs placebo 1.7% vs 1.6%; OR, 0.98 (95% CI, 0.27–3.49) Baricitinib 2 mg vs placebo (HZ) 1.2% vs 0.4%; OR, 2.34 (95% CI, 0.27–20.47) Baricitinib 4 mg vs placebo (HZ) OR, 3.88 (95% CI, 1.36 –11.06; <i>P</i> = 0.01)	5 (baricitinib 4-mg group): 3 NMSC, 1 breast, 1 lung 3 (placebo group): 3 NMSC, 1 breast, 1 ovarian	3 major adverse CVS events in the baricitinib 4-mg group and placebo and none in the baricitinib 2-mg group 4 thromboembolic events (PE, basilar and vertebral artery, peripheral thrombus, thrombophlebitis)	No increased risk of serious infections and HZ compared with placebo in the baricitinib 2-mg group No increased risk of serious infections vs placebo in the baricitinib 4-mg group but increased risk of HZ No malignancies reported in the baricitinib 2-mg group No thromboembolism reported in placebo group No reports of GI perforations
Tofacitinib						
Cohen et al, ⁷² 2017	Pooled analysis from RCTs	6194 19,406 patient-years exposure	Opportunistic infections including TB in 1.6% Active TB in 0.6% Serious HZ in 0.8% HZ Total, 11.3% Majority, 92% involved 1 dermatome	2.8% (excluding NMSC) 2% (NMSC)	GI perforation IR, 0.11 (95% CI, 0.07–0.17) 1.8% lymphopenia >500 and < 1000 cells/ μ L; crude IR, 3.4 (95% CI, 2.8–4.1)	Most common: AEs, nasopharyngitis, URTI, UTI SAE class, infections and infestations Serious infections, HZ, UTI, cellulitis
Verden et al, 2018	Observational/safety review of FAERS	—	—	—	PE: ROR, 2.46 (95% CI, 1.55 –3.91)	FAERS data indicated that pulmonary thrombosis may potentially be a class-wide issue for JAK inhibitors FDA warning regarding increased risk of PE and death when a 10-mg BID dose of tofacitinib was used in patients with RA (February 25, 2019) (https://www.fda.gov/ Safety/MedWatch/ SafetyInformation/ SafetyAlertsforHuman MedicalProducts/ ucm632016.htm)

AE = adverse event; CVS = cardiovascular; FAERS = US Food and Drug Administration's Adverse Events Reporting System; FDA = US Food and Drug Administration; GI = gastrointestinal; HZ = herpes zoster; IR = incidence ratio; JAK = Janus kinase; NMSC = non-melanoma skin cancer; OR = odds ratio; PE = pulmonary embolism; RCT = randomized controlled trial; ROR = reporting odds ratio; TB = tuberculosis; SAE = serious adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

experience including patients with moderate to severe RA, patients were willing to accept higher risks of AEs to achieve improved physical function and disease control.⁹⁷

Preferences of patients to take such treatments are also likely to be heterogeneous depending on their illness perception and treatment beliefs. Even a very low risk of SAEs with considerable morbidity such as serious infections, cancer, and rare events such as vasculitis-like events (Table 1) that may not be reversible after cessation of the drug may be of greater importance. A study of treatment preferences in patients with early RA (<2 years since diagnosis) reported that treatment benefits such as reducing the chance of joint damage and increasing the chance of symptom improvement were most important to patients. Of AEs, serious infection and possible increased cancer risk were deemed to be the most important, but patients were willing to accept a small increased risk for a 15% improvement in symptoms. However, there was a large subgroup of patients who were risk averse (54%), and in this group, the symptoms would need to improve by ~50% for patients to accept the small risk of infections and cancer.⁹⁸ The risk-tolerant group/benefit-driven group (46%) identified through latent class analysis were less likely to be taking oral csDMARD monotherapy. Expected factors such as education, higher household income, and age were not statistically significant in the multivariate model between risk-averse/risk-tolerant groups. Research on identifying features associated with perceptions of patients being risk-averse versus risk-tolerant would allow better targeting of preventative RA medications in high-risk individuals in the future.

Additional Factors in Future Decision-Making

The long-term outcomes when treating unclassified arthritis or individuals deemed at high risk of developing RA on the basis of their autoantibodies alone are not known. However, additional considerations in making such decisions include the possibility that treatment to prevent or delay RA may have the additional benefit of preventing future SAEs due to RA disease activity and their associated morbidity. Prevention of RA or reducing disease duration by delaying the onset may subsequently attenuate the risk of developing comorbidities directly associated with RA such as cardiovascular risk, interstitial lung disease, osteoporosis, and depression.

The reduction in multimorbidity and subsequent polypharmacy may itself have an impact on reduction of future SAEs; however, quantification of such benefits based on scientific evidence thus far is challenging. If shown, however, the benefits of preventative therapies would be considerable, both to patients in terms of improved long-term well-being and quality of life but also economically in terms of reduced costs for the health care systems.

Quantitative methods of benefit–risk assessment have been used by drug regulators such as the US Food and Drug Administration to evaluate therapies (eg, biologics).⁹⁹ Patient-focused benefit–risk assessment is based on weighing key benefits and harms of treatment based on clinical judgment, risk estimates, shared decision-making, and patient preferences. Several methods exist for assessing preferences such as structured-weighting (eg, direct weighting, ranking exercises), health-state utility (eg, time trade-off, standard gamble), stated-preference (eg, binary and discrete choice experiments), and revealed preference methods (patient-preference trials).¹⁰⁰ Combining RCT and real-world data from observational studies to develop quantitative personalized benefit–risk assessments to identify subgroups of patients who may be most likely to benefit from therapy may be feasible as shown in recent research.¹⁰¹ Application of techniques such as multicriteria decision analysis¹⁰² and ongoing methods development in this field would allow systematic assessment and quantification of benefits/harms that help inform patient perceptions and clinical decision-making. Combining these methods with existing risk calculators such as the Personalized Risk Estimator for Rheumatoid Arthritis,¹⁰³ along with effect and risk estimates from future trials/epidemiologic analyses, and patient preferences encompassing the heterogeneity of views would allow stratification of such treatments to the right subgroup of patients.

CONCLUSIONS

Antirheumatic medications used in clinically apparent RA disease have transformed the long-term outcomes of patients with RA over the last 20 years. Accompanying such treatments, however, is the considerable burden of AEs that may have a multiplicative or additive risk for certain safety outcomes such as infection when co-prescribed with other frequently administered medications in RA. Use

of csDMARDs and biologics, in the few published trials in subjects at risk of RA on the basis of laboratory abnormalities, have been associated with some SAEs, but the absolute risk is small. If such therapies prove effective at preventing or considerably delaying the onset of RA, incorporating patient preferences as well as robust quantification of benefits/harms would be vital. Serious infection and malignancy risk to treatments continue to be important considerations for individuals considering these treatments, and accurate estimates of events associated with morbidity in larger and more representative populations (without RA) would help informed decisions in the future.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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