Review

From clinical trials to the bedside: How can we treat patients with rheumatoid arthritis and concurrent morbidities who are generally excluded from randomised controlled clinical trials?

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ABSTRACT

In the last few years management of rheumatoid arthritis (RA) has changed substantially due to the availability of new drugs and newer therapeutical strategies. Controlled randomised clinical trials (RCT) have allowed us to analyse the efficacy and safety of all these innovative approaches. Unfortunately, these RCTs are not free from criticisms and their rigid inclusion and exclusion criteria may increase the differences between the ideal patients enrolled and the majority of patients seen in standard clinical care.

This review focuses on actual clinical practice, with particular attention on patient comorbidities and all the conditions which have been designated as exclusion criteria in the most important registration RCTs. We will attempt to provide an overview of the most widely used strategies in RA therapy.

Introduction

Rheumatoid arthritis (RA) is a chronic symmetric polyarticular disease sparing the axial skeleton except for the cervical tract (1). Recent advances in our understanding of the pathophysiology of RA have led to new therapeutical approaches, especially in consideration of the possibility of a "true window of opportunity", a period at the beginning of the disease during which early and aggressive intervention may alter the disease process, resulting in long-term, sustained benefits (2, 3). The management of RA has changed substantially, particularly with the immediate introduction of disease modifying anti-rheumatic drug therapy (DMARDs) as soon as the diagnosis is made – either a single drug alone at appropriately high doses or in combination therapy protocols. Rapid changes in DMARDs strategies have also commonly been adopted if disease remission, or at least significant improvement, is not reached (4-7).

Furthermore, innovative biological drugs are now available and their early use, alone or in association with traditional DMARDs, can quickly and markedly reduce the clinical and laboratory manifestations of the disease and also prevent joint damage and disability (8).

Acceptance of these new therapeutic options has been influenced by the results of several controlled randomised clinical trials (RCT) that have studied the efficacy and safety of various drugs. Unfortunately, these RCTs are open to criticism. There may be a significant gap between the "ideal" subjects enrolled in the studies and most patients seen in standard clinical care due to the rigid inclusion and exclusion criteria applied in RCTs (Table I) (9-23). Several major comorbidities have been identified as leading contributors to mortality in RA, including cardiovascular disease, infection, malignancy, gastrointestinal disease and osteoporosis, and these are often designated as exclusion criteria in RCTs, but their actual prevalence in RA patients is not yet well established (24). We therefore attempted to estimate the frequency of these conditions in a randomly selected series of 500 patients being followed in our clinic between 1990 and 2004, presenting our findings and the results published by others in Table II (25-35).

For each of the above-mentioned situations, in this paper we review the current literature and summarise the most broadly accepted therapeutic strategies.

Which is the best therapy for RA patients with hepatic disorders?

One of the side effects of DMARDs is

hepatotoxicity, which becomes a special concern in RA patients suffering from hepatic disorders (36). For this reason, among the exclusion criteria in most clinical trials are high transaminase levels (>1.2 times the upper limit of normal) and positive tests for HBs Ag or HCV Ab.

Immunosuppressive drugs may enhance viral replication, thus aggravating hepatitis B (HBV) and hepatitis C (HCV) viremia. The use of immunosuppressive drugs or glucocorticoids (GCs) has been linked to the re-activation of chronic HBV, leading in some cases to fulminant hepatitis (37, 38). In contrast, severe hepatic dysfunction and hepatic failure are less common in HCV-infected patients, probably due to a less marked cell-mediated immune response against the hepatitis C virus (38). The frequency of HBV and HCV in unscreened RA patients is quite high (39), and the identification of any previously undetected liver disease is recommended for all RA patients prior to the start of immunosuppressive treatment (40).

Mok *et al*. have recently shown that DMARDs, including some which were believed to be less hepatotoxic (such as hydroxycloroquine), may be associated with a high incidence of liver toxicity in RA patients with concomitant HCV infection. They concluded that in HCV patients DMARDs must be administered with caution and appropriate monitoring of liver function until further toxicity studies have been conducted (41).

The hepatotoxicity of methotrexate (MTX) has been widely investigated due to its position as an anchor drug in RA therapy. Low-dose MTX appears to have very few side effects in terms of liver toxicity. In fact, liver enzyme abnormalities, if they occur, usually do so within the first 4 months, are often reversible and do not require any change in therapy. It has been suggested, however, that higher doses may lead to the development of cirrhosis (42). The effect of MTX on chronic viral hepatitis also remains unclear. A few cases of fulminant HBV hepatitis after the withdrawal of MTX have been reported, suggesting that the restoration of immunocompetency could lead to a stronger immunologic attack against infected hepatocytes (43). It would appear logical to assume that in RA patients who are also positive for HCV or HBV, treatment with MTX could enhance the risk of hepatotoxicity and therefore most authors agree that MTX should not be used as a first-line therapy in patients with underlying liver disease. However a recent paper by Kujawska *et al*. suggests that the synergistic effect of MTX plus HCV on liver function may not kick in as rapidly as once feared and that therapy for up to one year will not necessarily result in cirrhosis (39, 41).

Only isolated cases of side effects from the use of leflunomide (LEF) in non-chronic viral hepatitis RA patients have been reported (42-47). Based on post-marketing surveillance data (over 80,000 patient-years of treatment) the incidence of hepatic failure seems to be 14 per 100,000 patient-years, i.e. no higher then that reported for other DMARDs (48, 49). No data on LEF in HCV-positive patients are available (50).

Cyclosporine A (CsA), another frequently used DMARD, is not directly toxic to the liver. Furthermore recent *in vitro* studies have demonstrated its anti-viral effect both in HCV replicon cells and in an HCV-infected cell line (51-53). In patients treated with CsA after a liver transplant for hepatitis C, conflicting results have been reported, possibly due to the capacity of CsA to suppress T lymphocyte function (thus permitting HCV viral replication), while its anti-viral effect plays no role

Table I. Comorbidities designated as exclusion criteria in the principal randomised clinical trials on rheumatoid arthritis.

Serious liver disease (transaminases more then twice upper normal levels)
HBV and HCV infection
Serious renal disease (serum creatinine > 2 mg/dL)
Cardiovascular disease (congestive heart failure, hypertension not controlled with a single drug)
Serious hematologic disease (hemoglobin level < 8.5 g/dL, platelet count < 100,000/mm^3, WBC < 3500/mm^3)
Pulmonary disease (active or past tuberculosis)
History of chronic infection or recent serious infection
Major surgery or severe infection less than 30 days before enrollment date
Lymphoma or other malignancy in the past 5 years
Female patient of childbearing age not using contraception
Age > 80 or < 19 years

Table II. The most significant comorbidities in 500 randomly selected RA patients being followed in our clinic between 1990 and 2004 and in similar studies in the literature.

	Prevalence		
Comorbidity	Our series		In the literature
HBV infection	9/500	1.8%	0–5% (ref. 25)
HCV infection	13/500	2.6%	0.6–7.6% (ref. 26, 27)
Serious liver disease*	10/500	2%	n.d.
Serious renal disease**	17/500	3.4%	n.d.
Pulmonary disease (active or past tuberculosis)	23/500	4.6%	3.6–17.2% (ref. 28, 29)
Cardiovascular disease	69/500	13.8%	11–13% (ref. 30-32)
Congestive heart failure	6/500	1.2%	3.9% (ref. 33)
Hypertension not controlled with a single drug	19/500	3.8%	n.d.
Misc. cardiovascular conditions	44/500	8.8%	n.d.
Lymphoma	1/500	0.2%	0.7%; relative risk 0.55 (ref. 35)
Other malignancy	16/500	3.2%	Relative risk 0.36–1.93 (ref. 35)

*Serious liver disease: transaminase levels more than twice upper normal values; **serious renal disease: serum creatinine > 2 mg/dL; n.d.: no published data.

in immunosuppression (53).

Finally, in a recent controlled trial on the efficacy of IFN and CsA in chronic hepatitis C, a combination of the two drugs was more effective than IFN alone and had an acceptable safety profile (52). It should be noted that, while CsA represents a potentially safe DMARD, the results obtained in liver transplant patients cannot be directly extrapolated to chronic rheumatic disease and no trials have yet been conducted on HCV-positive RA patients.

In the 1990s tumour necrosis factor antagonists (anti-TNFα) for the treatment of RA were introduced. The aggravating effect of TNFα on viral infection is not clear; different results have been reported depending on the experimental model and virus used (54). These new drugs do not appear to be directly toxic to the liver, and the administration of infliximab in patients with Crohn's disease plus HCV was not associated with progression of their viraemia or hepatitis (55, 56). Peterson *et al*. examined the data on 24 HCV RA patients who had taken anti-TNFα for at least 2 months and found that liver function and the HCV viral load did not worsen over a median period of 9 months, suggesting that TNFα does not suppress HCV infection. Marked variations in response to the drug were seen in a few patients, however, leading the authors to recommend the careful monitoring of HCV viraemia and to consider discontinuation of the drug in those patients who show a rise in HCV viraemia levels (57).

More recently, 5 HCV-positive RA patients were treated with anti-TNFα and followed up for a period of 41 months; retrospective review of their aminotransferase serum levels and viral load showed only transiently raised hepatic enzyme levels during anti-TNFα therapy, and a decreased viral load after long-term treatment in one patient (58). Similar data were reported in 2 patients by Oniankitan *et al*. (59). Currently available data suggests that chronic viral infection (*i.e*., HIV or HCV) does not constitute a definite contraindication for anti-TNFα treatment.

One of the most recently introduced DMARDs is mofetil mycophenolate (MMF), and very little data is available regarding its effects in RA. Its supposed anti-viral properties are based on anti-rejection studies conducted in transplant patients, one of which recently showed significantly decreased transaminase levels after orthotopic liver transplantation (60). This possible anti-viral effect remains to be confirmed however, in studies on RA patients with HCV. The above concepts are summarized in Table III.

Table III. Hepatotoxicity and DMARDs.

Less hepatotoxic	More hepatotoxic
CsA	MTX
Anti-malarial drugs	LEF
Anti-TNFα	
MMF	

Which is the best therapy for RA patients with concomitant renal disorders?

Renal involvement in RA is relatively common and clinically significant because it can severely affect the course and mortality of the primary disease. Kidney damage during RA may be due to amyloidosis, rheumatoid nephropathy or the nephrotoxic effects of DMARD and nonsteroidal anti-inflammatory drug (NSAID) treatment (61). Renal amyloidosis, which occurs in approximately 5% of RA patients, may lead to severe renal failure. Mesangial glomerulonephritis is the most frequent histological sign, followed by acute or chronic interstitial nephritis. However, renal complications in RA patients are usually a side effect of therapy with drugs such as NSAIDs, gold salts and CsA. The fear that these drugs might worsen kidney function in patients with pre-existing renal disease has severely limited their use and patients with baseline serum creatinine levels ≥ 2 mg/dl have been excluded from clinical trials (62).

MTX, LEF, anti-malarials and biologic drugs seem to have little or no toxicity and are used as the first-line therapy in RA patients with kidney disorders. MTX may induce a slight decrease in renal filtrates but with no change in serum creatinine levels. Occasionally, and in a dose-dependent manner, acute tubular necrosis may develop (63, 64). A recent study demonstrated that low dose MTX did not lead to impaired renal tubular function, even when used with non-salicylic acid anti-inflammatory drugs (NSAIDs) (65). Rare cases of IgA nephropathy during treatment with LEF or TNF blocking receptors have been reported in patients with longstanding RA (66). Nevertheless in a recent evaluation of the effect of TNFα blockers on renal function, no alterations in the indices of early tubular injury were noted after infliximab infusion (67).

CsA is a highly effective immunosuppressive agent both for the advanced and early stages of RA, but some nephrotoxicity (defined as an increase in the serum creatinine concentration) that is partially irreversible at doses ≥ 5 mg/Kg/day has been demonstrated. In patients with compromised renal function, reducing the dosage is imperative since increases in creatinine levels are clearly dose-dependent. Reliable predictors of nephrotoxicity have not been identified, but the profile of patients at increased risk of chronic irreversible CsA nephrotoxicity includes advanced age, a prior decrease in the glomerular filtration rate, high daily doses (>5 mg/Kg/day) for a prolonged period (> 6 months) or the concurrent use of nephrotoxic agents, in particular NSAIDs. The latter may increase renal side effects in a small number of RA patients by inhibiting prostaglandin synthesis in the kidney, so tapering of the dose is strongly recommended (62).

In summary, the drugs that may be used in RA patients with renal disorders include MTX, LEF, anti-malarials and anti-TNFα agents. Drugs to be avoided are NSAIDs, CsA and gold salts. These findings are summarised in Table IV.

Table IV. Nephrotoxicity and DMARDs.

Less nephrotoxic	More nephrotoxic
MTX	CsA
LEF	Gold salts
Anti-malarial drugs	NSAIDs
Anti-TNF	

Which is the best therapy for RA patients with cardiovascular disease (CVD)?

CVD is considered to be the leading contributor to mortality in RA, accounting for approximately one-third to one-half of all RA-related deaths (68). The pathogenesis of CVD in RA is multi-factorial and both the inflammatory mediators intrinsic to RA and the drugs used for its control may promote the development of accelerated atherogenesis. Further potential risk factors specific to RA include hyperhomocysteinemia, diminished exercise capacity, dyslipidemia and vascular inflammation. In particular, it has been suggested that subclinical vasculitis may lead to endothelial injury and accelerated atherosclerosis (69, 70). Among the inflammatory mediators involved in CVD, C-reactive protein (CRP) plays a leading role, activating components of the complement cascade involved in early atherogenesis (71).

Among the drugs used to treat RA, NSAIDS, LEF and CsA and GC may lead to, or aggravate already existing, hypertension (72, 73). GC may lead to hyperglycemia and hyperlipidemia (74). The role of dyslipidemia in RA is somewhat contradictory; some studies have shown an oscillation in serum lipid levels depending on the duration and/or severity of the disease while others have reported significantly lower levels of total serum cholesterol in severe active RA. The last finding, however, could be explained by the malnutrition and cachexia seen in advanced RA. It is interesting to note that hydroxychloroquine (HCQ) has a favourable effect on serum lipids, and may offer an alternative therapy for patients at risk of CVD (75).

MTX therapy results in increased serum homocysteine levels, which have been linked to coronary artery thrombosis. However, folic acid lowers serum homocysteine levels and may be protective in patients receiving MTX (76, 77).

TNF has been presumed to play a crucial role in causing new congestive heart failure or in worsening pre-existing disease (78). Various pathogenetic mechanisms have been hypothesised, such as direct negative inotropic effects on the myocardium, the induction of myocardial fibrosis, an alteration of myocardial matrix proteins and the facilitation of a viral myocarditis (79). Nonetheless, while data from cardiac heart failure trials suggest no cardiac benefit, but also potential negative consequences of TNF inhibitor use, utilisation of anti-TNFα in patients with RA does not appear to contribute to incident cardiac heart failure even if TNF inhibitors in patients with pre-existing cardiac heart failure have not been extensively studied. Until further studies become available, it may be prudent to avoid the initiation of TNF inhibitors in patients with pre-existing NYHA class III or IV disease or unstable heart failure (78, 79).

In conclusion, due to the contribution of CVD to mortality in RA patients, it is crucial in clinical practice to individuate those patients at highest risk and concentrate on primary and secondary preventive measures. The relative toxicities of different RA drugs in cardiac patients are presented in Table V.

Table V. Cardiotoxicity and DMARDs.

Not cardiotoxic
Anti-malarial drugs
Less cardiotoxic
LEF, NSAIDs, GC, CsA, MTX
More cardiotoxic
TNF inhibitors in patients with pre-existing NYHA Class III or IV disease or unstable heart failure

Which is the best therapy for RA patients with infections?

Infection is a major cause of RA-associated morbidity, with RA patients disproportionately predisposed to pulmonary infections, generalised sepsis, osteomyelitis, cellulites and septic arthritis (80). As with other co-morbidities it is difficult to distinguish between the intrinsic effects of RA and the iatrogenic effects of agents used in RA treatment (69). In fact, RA itself can lead to alterations in cellular immunity such as a decrease in the number and function of T-suppressor and natural killer cells (81). The immunosuppressive drugs used to treat RA (DMARDs, glucocorticoids, biological agents) probably increase this risk due both to their potential myelosuppressive effect and to the inhibition of cellular and humoral immunity. This is particularly true with regard to the risk of post-operative infection, especially after orthopaedic procedures. In such cases, temporary discontinuation of DMARDs is usually recommended in clincal practice (69).

Concerning glucocorticoids and infection, while a link between high-dose steroids and serious infections has frequently been described, the precise risk associated with the low-dose, daily therapy typically used in RA has not been clearly defined (82). Few studies on the rates of infection in RA patients treated with corticosteroids have been published. However, an extensive meta-analysis involving patients with a variety of conditions suggests that there is no increased risk for infection with prednisone doses < 10 mg daily or a cumulative dose of < 700 mg (69).

The recent introduction of anti-TNFα agents has raised new issues regarding the potential role of these agents in predisposing to infection. The best available evidence, mostly from randomised controlled clinical trials, suggests that there is no overall increase in the incidence of serious infection with these agents. Nevertheless, published results based on post-marketing data have specifically suggested an association between anti-TNFα and an increased incidence of tuberculosis (TBC). This data suggests that TBC infection may be related to blockade of TNFα due to the role played by this cytokine in granuloma formation. Blockade of interleukin-1 activity with anakinra appears instead to be relatively safe (82).

A careful screening for TBC is therefore recommended before starting biological agents (83). TBC re-activation or even primary tubercolosis may even be associated even with long-term therapy with corticosteroid or other immunosuppressive drugs since a handful of cases of primary TBC associated with the use of low-dose MTX have been reported as well (84). All of these data justify a thorough screening and prophylaxis with isoniazid in rheumatic

patients who have taken immunosuppressive drugs, especially in countries where tuberculosis is endemic (85).
In patients who develop TBC during anti-TNF therapy, the drug should be immediately stopped and four-drug therapy for TBC started (86). No data are available in the literature regarding the concomitant use of anti-TNF and TBC therapy in tuberculosis patients, while the concurrent use of other DMARDs (AZA, CsA) seems to be effective (87).
In addition to cases of TBC, many other infections have been reported after the use of TNF-alpha inhibitors, including bacteria such as *Listeria, Nocardia, Streptococcus pneumoniae, Legionella, Escherichia coli, Staphylococcus lugdunensis, Proteus mirabilis, Staphylococcus aureus, Peptostreptococcus, Streptococcus pyogenes,* and *Salmonella typhimurium*; fungi including *Histoplasma, Pneumocystis jiroveci, Aspergillus, Cryptococcus, Candida albicans, Coccidioides,* and *Sporothrix*; and viruses including parainfluenza type 3 and cytomegalovirus (88).
In Table VI we summarise the management of RA patients who develop infections.

Table VI. Recommended modifications in drug therapy in RA patients who develop concurrent infection.

1. Immediately stop immunosuppressant drug (anti-TNFα, MTX, CsA, AZA) and institute infectious treatment

2. Institute infectious treatment without stopping immunosuppressant treatment with antimalarial drugs, anakinra, LEF, SZP

What is the risk of malignancy in RA patients?

The question as to whether RA increases the risk of certain types of malignancy is stilll being debated and conflicting data have been reported on this subject. Nevertheless, there is an accumulating evidence that RA patients are substantially more likely to develop lymphoproliferative malignancies, including lymphoma, leukemia and multiple myeloma. At the same time, RA patients consistently seem to have a lower risk of gastrointestinal-related malignancies (35). The cause of the observed increase in lymphoproliferative malignancies is unknown but many factors are considered to be involved, from the immunological modifications directly induced by RA (i.e. clonal expansion of CD5+ cells and decreases in T-suppressor lymphocytes and natural killer cells) to the effects of immunosuppressive drugs and the presence of comorbid conditions (i.e. Sjögren's syndrome) (89).
Immunosuppressive agents implicated in RA-related malignancies include MTX, AZA, CsA and cyclophosphamide and mechanism is thought to lie in the chronic immunosuppression that develops in lymphomas, as described in the acquired immune deficiency syndrome or in patients receiving immunosuppressive therapy after solid organ transplantation (69). Nonetheless, the association between conventional drugs and malignancy is relatively weak at most. The possibility that patients treated with TNFα antagonists may run a somewhat higher risk for lymphoma than in patients not treated with such agents must be kept in mind, but current practice recommendations should probably go no further than a vigilant awareness of the possibility of lymphoma in any RA patient who exhibits unexplained systemic symptoms.
In conclusion, in clinical practice the onset of new constitutional symptoms (i.e., fever, chills, night sweats, anorexia) in the absence of infection or significant RA disease flare should raise the suspicion of lymphoproliferative malignancy and appropriate tests should be undertaken (90).
The proper management of RA in patients with concomitant neoplastic disease is still under discussion and, since no absolute contraindication to the use of immunosuppressants has been found, each case needs to be carefully evaluated in a multi-disciplinary approach involving both the rheumatologist and the oncologist.

Which is the best therapy for RA patients with concomitant gastrointestinal disease ?

Upper gastrointestinal (GI) diseases are increased in RA patients and are attributable to the GI-toxicity of NSAIDs and GCs. No data are available concerning DMARD use and gastrointestinal toxicity (91). In contrast to the other co-morbidities, moreover, there is no evidence that RA itself causes GI problems. By inhibiting the COX-1 isoenzyme, NSAIDs interfere with normal prostanoid-dependent mucosal protection and may subsequently lead to ulceration and perforation of the GI mucosa (69). This toxicity may be enhanced by the concomitant use of glucocorticosteroids that, however, independently increase GI events (92). In conclusions, in clinical practice the dosage of NSAIDs and GCs should be reduced and a gastroprotective agent given, especially in patients most at risk for GI-related adverse events.

Which is the best therapy for female RA patients of childbearing age and during pregnancy?

The interaction between anti-rheumatic drugs and reproduction is quite complex and raises many questions concerning both the impairing effect of such therapies on fertility and the side effects of these drugs during pregnancy and lactation (93).
Most anti-rheumatic drugs have no effect on the gonads. However some of them – particularly NSAIDs and GC – can interfere with prostaglandins and ovulation and cause reversible infertility. Others, such as methotrexate and sulfasalazine, carry a risk of gonadotoxicity and chromosomal defects and interfere in particular with male fertility (93-95).
Several case reports and small series have described transient infertility following treatment with indomethacin, diclofenac, piroxicam and naproxen (96,97). These agents in fact may block follicular rupture or inhibit tubal motility by a prostaglandin synthesis inhibition (94). Oligospermia and azoospermia have been linked to sulfasalazine (SZP) and methotrexate treatment, while azathioprine does not impair male reproduction (94). Unfortunately it is not possible to predict which patients will become sterile nor is there a clear correlation with the dose. Never-

theless it must be said that oligo- and azospermia occur only rarely during therapy with MTX and are reversible after discontinuation of the drug. SZP-induced sperm alterations are reversible as well an average of 2.5 months after discontinuation of the drug (98).

With regard to the effect of anti-rheumatic drugs on pregnancy, virtually all the drugs may affect fetal development and may cause specific complications in the mother. Furthermore, it must be kept in mind that the first trimester, when organogenesis is most active, may be the period of greatest risk in terms of side effects, but as the patient approaches labor and delivery other risks arise. The second trimester appears to be the safest time for the administration of most therapeutic agents (94).

The two questions most frequently asked are: (1) whether immunosuppressive treatment should be stopped before a planned pregnancy; and (2) which drugs can be used for the control of disease activity during pregnancy (99, 100)?

Concerning the first question, the terato- and embryotoxicity of MTX and LEF have been clearly demonstrated; these drugs therefore are contraindicated during pregnancy and should be prescribed to fertile women only with safe contraception (101). MTX-induced congenital defects include craniofacial and limb defects and central nervous system abnormalities including anencephaly, hydroencephaly and meningomyelocele (102). Due to the possibility that active metabolites may remain in cells or tissues for about two months after the cessation of therapy, women who wish to become pregnant should discontinue treatment with MTX for at least 3 months prior to attempting conception (101). Skeletal and central nervous system malformations have been observed with LEF as well (103). Considering its long half-life, elimination of LEF can be accelerated by cholestyramine or active choarcol (101).

With regard to the second question – which drug treatment may be used for the control of disease during pregnancy – it must be kept in mind that the majority of women with RA show improvement of their disease symptoms during pregnancy. Therefore, continuation of drug treatment is necessary in only 10-25% of pregnant RA patients (101). In such cases, GCs are the drug of choice (99). Prednisone, prednisolone and methylprednisolone are preferred for the treatment of maternal disorders, since they are metabolized by placental 11-hydroxygenase so that the fetus is exposed only to appoximately 10% of the maternal dose. On the contrary, when GC are needed to treat fetal conditions (i.e., immature lungs), fluorinated preparations such as dexamethasone and betamethasone are preferred because they are less metabolized by the mother and therefore more available to the fetus (99).

GC are considerated to be safe at any time during pregnancy but are associated with some maternal and fetal complications. In addition to its regular side effects, GC may cause pregnancy-specific complications such as premature rupture of the membranes, exacerbation of gestional diabetes and hypertension, and fetal complications such as adrenal suppression and infection (104). Fortunately, due to the fact that only a small percentage of the maternal dose of rapidly acting GC reaches the fetus, the incidence of adrenal suppression and infection seems to be quite low (99). Finally no adverse effects have been reported from the use of GC during lactation (99).

In conclusion, the use of GCs is considered to be safe during both pregnancy and lactation. Supplementation with oral calcium and vitamin D is recommended to prevent osteoporosis and, in addition, a patient who has been treated with GC during pregnancy should be given "stress doses" of GC for any emergency surgery, cesarean section, or prolonged labor and delivery (99).

The effects of immunosuppressive drugs such as HCQ, AZA, CsA and SZP on pregnancy and lactation, as reported in the literature, deserve separate consideration. There are no reports of adverse effects of HCQ on fertility. HCQ crosses the placenta and in theory could accumulate in the fetal uveal tract. To date, however, there have been no reports of congenital malformations in children exposed to this drug during gestation when used to treat a mother with either RA or SLE (99). Nevertheless, while in pregnant SLE patients continuing HCQ may be justified because the risk of lupus flare represents a greater danger than the therapy, it may be prudent to replace HCQ with GC during pregnancy in patients with RA. Moreover, small amounts of HCQ have been found in breast milk and therefore breastfeeding during HCQ therapy should be undertaken cautiously (99).

Many pregnant patients with renal transplants, hematological malignancies, inflammatory bowel disease or SLE have been treated with AZA. No effect on fertility, reported increase in abortion or definite association with teratotoxicity in humans have been reported (99). Indeed, the fetal liver lacks the enzyme that converts AZA into its active metabolites and this deficiency seems to protect the fetus from any teratogenic effects early in pregnancy. Nevertheless, since a variety of adverse effects have been described during pregnancy (such as fetal growth retardation and infection), use of AZA should be reserved only for the most severe cases (99). Because of potential immunosuppression lactation is not recommended either (99).

Experience with CsA in pregnant RA patients is limited. Most of the reported data involve pregnant transplant patients. In these cases, although the risk of congenital abnormalities is not increased, some maternal side effects, including hypertension pyelonephritis and seizures, have been reported. In general CsA, like AZA, should be reserved for the most severe cases. The drug is also contraindicated in lactation (95, 99).

Data on the use of SZP in pregnancy originates particularly from cases of patients with inflammatory bowel diseases. In such patients, SZP does not seem to cause an increase in the incidence of either fetal abnormalities or spontaneous abortion (95, 99). As the drug is excreted into breast milk, its cautious use during lactation is recommended (99).

Finally, there is no consensus regarding anti-TNF alpha antagonists since there

Table VII. Adverse effects of DMARDs on fertility, teratogenicity and lactation.

No adverse effects on fertility: AZA, HCQ, CsA
Potentially adverse effects on fertility: NSAIDs, GC, MTX, LEF, SZP
No teratogenicity: AZA, CsA
Teratogenicity unknown: Anti-TNF
Proven teratogenicity: LEF, MTX
Potentially adverse effects during lactation: HCQ, SZP
Proven adverse effects during lactation: CsA, AZA, LEF, MTX

are no controlled trials of TNF inhibitors in pregnant women. Reports on the post-marketing experience of Crohn patients treated with infliximab during pregnancy suggests that infliximab may not have altered pregnancy outcomes in this observational study. However, until further studies are performed, physicians must be cautious and discuss reliable birth control methods with their female patients (105). Concerning adalimumab, an embryonic–fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages of up to 100 mg/kg and has revealed no evidence of harm to the fetus caused by this drug. Nonetheless, adalimumab has not been studied in pregnant women and should be used during pregnancy only if clearly needed (106). The different toxicities, in terms of fertility, teratogenicity and lactation, of the drugs most commonly used to treat RA are presented in Table VII.

Which is the best therapy for elderly patients?

RA among the elderly is a subject of increasing importance nowadays due to the recent growth in the proportion of older persons in the general population. Controversy has surrounded the question as to whether RA afflicting the elderly is a different disease than RA in younger patients. Some studies have suggested that elderly-onset RA is characterized by a more equal sex distribution, a more acute disease onset, a greater tendency for large joint involvement, markedly raised ESR, and a more favourable prognosis. However, the studies on this subject are not conclusive (107-111). In fact, even if elderly patients present with more severe joint involvement at disease onset, it seems that age at disease onset does not influence the clinical course and outcome of early RA patients (112).

Indications for therapy in the elderly are almost the same as in younger patients even if toxic side effects are probably more common in the elderly, necessitating close supervision. Moreover, several age-related factors need to be carefully considered including concomitant diseases, existing medication, drug compliance, and altered age-related physiology and pharmacokinetics. Due to all of the above-mentioned considerations, people over 75 years are usually excluded from clinical trials.

Nonetheless, since in the elderly even a small loss of physical function may have a markedly detrimental effect, leading to the development of other pathological conditions it is quite important to treat patients effectively to preserve physical function as much as possible, while in younger patients the principal target is to induce pain relief (113). MTX, due to its efficacy and its acceptable toxicity profile, is the most widely used DMARDs for the treatment of older RA patients in the US and Europe. However, if not tolerated, the most popular alternative DMARDs are HCQ or SZP for mild-to-moderate disease and CsA or LEF for severe disease, given in combination with low-dose oral corticosteroids (114). New biological drugs have also been employed in some cases, at the same dosages as in young adults (115).

Anti-rheumatic drugs and osteoporosis

RA is characterized by juxta-articular osteoporosis, but also systemic bone loss is caused by increased osteoclastic activation, so that osteoporosis and RA are often "twin brothers". The generalized bone pathogenesis is multi-factorial, with both non-disease-specific (age, female sex, postmenopausal status) and disease-specific factors (cytokines, reduced physical activity, disease activity, GC use) involved. Furthermore, some studies have linked the use of DMARDs (MTX and CsA) to bone loss (116).

The negative effect of MTX on bone mineral density is well known. The classic triad of osseous pain, osteoporosis and stress fractures (to the distal tibiae), reversible after discontinuation of the drug, was first described in children with leukemia who were treated with long-term, low-dose maintenance MTX therapy (117). Some other similar cases have been described (118-120) and the dose-dependent inhibition of osteoblast proliferation represents one of the proposed mechanism for MTX-induced osteopathy. Such osteopathy has been reported in RA and psoriatic arthritis patients as well. More recently, El Mediany *et al*. (121) demonstrated a reduction in deoxy-pyridinoline and an increase in bone alkaline phosphatase after 9 months in female RA patients being treated with MTX 10-15 mg/week. Similar results were found in a longitudinal study in a larger RA patient cohort (122), although no adverse effect on bone turnover markers were demonstrated; in the same study biopsies (done before and after low-dose MTX treatment) in 4 patients showed no negative effect of MTX on bone.

The positive effect of MTX on disease activity and inflammatory signs may also help to control and reduce bone loss in RA patients, as shown by Buckley *et al*. (123), who measured bone mineral density in a prospective randomised, placebo-controlled trial on patients receiving different DMARDs including MTX. Other studies showed a similar effect on BMD in groups taking MTX versus those not taking DMARDs (122, 124, 125). Finally, a large multicenter cross-sectional study (126) demostrated that MTX use was not an independent predictor of BMD.

In conclusion, by interfering with inflammatory cytokine production and activity (i.e. IL1 and TNFα, which are osteoclastic stimulators), MTX at the low doses used in RA may have a protective effect on bone mass and turnover. The effect of high doses and the use of MTX in non-active disease still

need investigation.

CsA represents another widely used DMARD in transplant and RA patients. Animal models show severe, rapid, dose- and time-dependent bone loss (127). There is probably a multiple pathogenetic pathway for CsA-induced bone loss. CsA may reduce creatinine clearance, leading to a reduction in calcium intake (by $1,25(OH)_2D$ reduction) and then an increase in PTH. The second path could involve a reduction in sex hormone levels with a consequent increase in bone turnover. Finally, CsA causes a reduction in the synthesis of osteoprotegerin mRNA, and hence an increase in osteoclast activation and resorption. Studies on bone loss in kidney transplantation (128, 129) demonstrated a rapid bone loss in patients taking CsA due to high turnover. The use of CsA in rheumatic patients at doses < 5mg/kg has not been associated with clinically significant adverse effects on bone and the addition of CsA to MTX in MTX-resistent RA patients resulted in an increase in BMD (130), reflecting the improvement in acute phase reactants.

Some data are available on anti-malarial drugs which accumulate in bone and, concentrating at the osteoclast-bone interface, could interfere with bone resorption (131). This could be the mechanism underlying the decrease in bone resorption that Julkunen *et al*. showed in histologic samples in 1976 in RA patients treated with antimalarials (132).

LEF has a direct effect on the receptor activator of NF-kb ligand (RANKL)-mediated osteoclast differentiation by inhibiting the induction of the nuclear factor of activated T cell c1 (NF-AT c1), the master switch regulator for osteoclast differentiation, but to date no clinical studies has been carried out on the effect of leflunomide on BMD in RA patients (133).

Table VIII. Osteoporosis and DMARDs.

No data: SZP
Probably safe to use:
LEF (no clinical studies on BMD)
Tacrolimus
CsA (at doses < 5 mg/Kg/day)
MMF
AZA
Safe to use:
MTX (at low doses in active disease)
Anti-malarials drugs
Anti-TNFα

In recent years new biological drugs have been more widely used and studied. As TNFα and IL-1 are potent stimulators of bone resorption, their inhibition may have a positive effect on bone and some data on markers of bone turnover are now available. Infliximab has been demostrated to reduce the urinary excretion of pyridinoline and deoxypyridinoline during RA therapy, showing significant changes at month 9 with respect to basal values (134). Another recent study showed a significant decrease in bone markers (consistent with a reduction in serum levels of acute phase proteins) after 30 and 46 weeks in 22 patients with RA treated with infliximab for 46 weeks (135).

A positive effect on bone mass, with a tendency to an increase in lumbar BMD, after one year of treatment with infliximab in RA patients has been shown in an uncontrolled longitudinal study (136), but at the same time a low decrease in femoral BMD was observed. On the contrary, in a 12-month study of RA patients treated with infliximab, Lange *et al.* reported a significant increase in femoral BMD and a trend towards improvement in the spine (137). In the same study, a significant decrease in the marker for bone resorption was registered. A positive effect in spine and hip BMD (and in bone turnover markers) of anti-TNFα (infliximab, etanercept or both) has also been recently shown in uncontrolled longitudinal studies in patients with spondyloarthopathies (138-140).

Tacrolimus did not induce severe osteoporosis and MMF produced no change in trabecular bone volume in a rat model (141, 142). Above all, tacrolimus showed a more favourable long-term effect on bone mass than CsA in humans after liver transplantation (143). Azathioprine has shown no effects on bone volume in the rat model (144). Table VIII summarises what is known regarding the enhanced risk of osteoporosis in patients taking DMARDs for RA.

From the bench to the bedside: Further considerations on drug interactions

The overall impact of co-morbidities in RA patients deserves consideration, not only because of the side effects of DMARDs, but also with regard to drug interactions. Interactions are possible whenever a patient takes two or more medications concurrently and there are a number of mechanisms by which drugs may interact. From a practical point of view, most of these may be classified as either pharmacokinetic or

Table IX. Drugs that cause alterations in DMARD levels.

	Drugs which, when administered concommitantly, can modify serum levels of DMARDs	
	Raise serum levels	Lower serum levels
DMARDs		
Methotrexate	§ Penicillin Methylprednisolone	* Tetracycline, cloramphenicol ° Phenylbutazone, p-aminobenzoic acid, diphenylidantoin, salicylic acid
Cyclosporine	†Ketoconazole, erythromycin, amphotericin B, propaphenone, diltiazem, nicardipine, verapamil, oral contraceptive	†Carbamazepine, phenitoin, metimazol, rifampin, phenobarbital, trimethoprim-sulfamethoxazole

§Reduced renal clearance; °effect on the binding protein of MTX, *reduced intestinal absorption; † hepatic P450 systems.

Table X. DMARDs cause alterations in levels of the following drugs.

	When taken concommitantly with DMARDs, the serum levels of these drugs may be affected	
	Serum levels increase	Serum levels lower
DMARDs		
Methotrexate	Theophylline*	
Cyclosporine	Prednisolone*	
Leflunomide		°Phenitoin, warfarin, tolbutamide,
Sulphasalazine		Folic acid, digoxin
Azatioprine	†Succinylcholine (depolarizing drugs) allopurinol, thiopurinol	†Tubocurarine (non-depolarizing drugs)

*Reduced renal clearance; °CYP2C9 system; †unknown.

pharmacodynamic interactions. In pharmacokinetic drug interactions, one drug affects the absorption, distribution, metabolism, or excretion of another. In pharmacodynamic drug interactions, two drugs have additive or antagonistic pharmacologic effects. Either can result in adverse effects. Tables IX and X summarise the most common drug-to-drug interactions described for DMARDs and their hypothesized pathogenetic mechanisms. While marked advances have been made in the study of the mechanisms of drug interactions over the past few decades, there is still much to learn and thus many of the concepts useful today will be refined in the future. It also should be kept in mind that for some drug-drug interactions more than one mechanism may be at work simultaneously.

Conclusions

Today many effective treatment for RA are available, but the results of RCTs cannot be applied directly to clinical practice. Drug therapy must be tailored to the individual patient, taking into consideration not only disease activity but also other factors such as the age of the patient, his/her preferences, the presence of comorbidities, possible interactions with concurrent drug therapies, and the medical experience of the clinician. All of these factors are particularly important in conditions that have been excluded from the RCTs. Nonetheless, promising results are coming from pharmacogenetical studies and it is likely that in the near future the gap between the ideal patient and the real patient will be lessened, with a better standardisation and a further optimisation of medical treatment.

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