Review

Therapeutic drug monitoring in rheumatic diseases: utile or futile?

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Abstract

Rapid and effective suppression of inflammation is a primary goal in the treatment of rheumatic diseases. However, the therapeutic effect of most medications may be slow to manifest, in the order of weeks or months in the case of DMARDs. Monitoring of drug concentrations allows the possibility of appropriate dose adjustment or changes in medication to achieve more rapid or better outcomes. We review the evidence for drug concentration monitoring. Despite the theoretical utility for monitoring of MTX polyglutamate concentrations in red blood cells in patients with RA, studies have not shown a clear association between concentrations and either efficacy or toxicity and routine measurement is not yet recommended. Small studies associating disease control with concentrations of anti-TNF therapies and anti-drug antibodies suggest that routine monitoring may be useful in the future. However, the data are not yet sufficient for this recommendation. With the use of allopurinol in gout, there is a putative therapeutic range for the active metabolite oxypurinol; however, adjusting the allopurinol dose to achieve a target urate concentration is likely to be most effective, and measuring oxypurinol may be best suited to assessing drug adherence. Although measuring thiopurine metabolite concentrations with AZA therapy has been shown to be useful in IBD, studies in rheumatic diseases have so far failed to confirm a useful association between concentrations and disease control or drug toxicity. Whole blood concentrations of HCQ have been associated with disease control in SLE and future studies may be able to determine a therapeutic range.

Key words: therapeutic drug monitoring, methotrexate, allopurinol, rheumatology.

Introduction

Rapid and effective suppression of inflammatory disease activity in order to prevent irreversible joint or organ damage is a primary goal in the management of many rheumatic diseases. However, most DMARDs take some months to become effective and not all patients will respond to an individual DMARD. In RA, early introduction of DMARDs, early use of combination therapy, frequent disease activity assessment and therapeutic changes if necessary are all recommended with the aim of rapid disease control [1, 2]. However, these approaches still require the passage of time before a response can be determined, and even if the desired therapeutic effect is achieved, the patient may discontinue therapy due to the occurrence of adverse effects.

Pharmacogenomics and therapeutic drug monitoring (TDM) are two methods that may help determine whether an individual patient will respond to or have adverse effects associated with a particular drug. Within the field of rheumatic diseases only two pharmacogenetic tests have reached clinical practice. The thiopurine methyltransferase genotype has been associated with adverse effects to AZA [3] and HLA-B*5801 has been associated with allopurinol hypersensitivity syndrome (AHS), particularly in Asian populations [4]. TDM has received less attention and is the subject of this review.

Therapeutic drug monitoring

TDM is the use of measured drug concentrations to alter therapy to improve drug efficacy and/or reduce toxicity. It has particular benefits for drugs with a low therapeutic index where the difference between clinically effective concentrations and concentrations associated with adverse effects is small. Defining treatment targets in rheumatic diseases [e.g. 28-joint DAS (DAS28) in RA and serum
urate (SU) in gout] enables clear outcome measures on which to base TDM guidelines.

There are numerous variables that can influence drug concentrations, including dose, route of administration, concomitant medications and the clinical status of the patient, such as age, BMI and renal and hepatic function. The current approach to dosing of most DMARDs uses a fixed one-size-fits-all approach whereby patients receive the same, or similar, dose regimen regardless of age, gender, weight, BMI or other variables that might influence drug clearance. It is highly likely that drug efficacy and tolerability could be improved in some patients by altering the dose or dose interval, based on patient characteristics and measurements such as trough drug concentration and/or the presence of anti-drug antibodies in patients receiving biologic agents. This is also likely to result in a better cost–benefit ratio for some medications, which may be particularly relevant for the biologic agents, which are expensive. Such parameters may also allow for a more informed approach towards the continuation or cessation of a particular DMARD. This review will summarize data available on TDM in rheumatic diseases with a focus on MTX, allopurinol and the biologic agents for which there are currently the most data.

MTX in RA

MTX is the anchor drug in the management of RA and is also used in other forms of inflammatory arthritis. The dose of MTX required by individual patients to provide the desired level of disease control in RA varies greatly and is largely unpredictable. The ability to use MTX concentrations to determine whether the best therapeutic approach is to increase the dose of MTX or to change to an alternative or combination DMARD or biologic therapies would be a major advance. It has been suggested that measurement of red blood cell (RBC) MTX polyglutamates (MTXGlu₃) could be useful in this role.

**MTX polyglutamates: pharmacology**

Once absorbed, MTX is taken up rapidly from the plasma into a variety of cells. Intracellularly, up to four additional glutamate (GLU) moieties are added to MTX by folylpolyglutamate synthetase. Terminal MTX GLUs are removed by γ-glutamyl hydrolase, returning MTX to its monoglutamate form, which is rapidly transported out of the cell by multidrug resistance proteins (Fig. 1).

The long-chain MTX polyglutamates (MTXGlu₃₋₅) are thought to be responsible for most of the anti-inflammatory effects of MTX. They inhibit several important intracellular enzymes, including dihydrofolate reductase, resulting in decreased DNA methylation, and thymidylate synthase, interfering with DNA synthesis, and 5-aminomimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, which ultimately inhibits production of proinflammatory cytokines including TNF-α, IFN-γ and IL-1 (Fig. 1).

**MTX polyglutamates, disease activity and adverse effects**

Plasma MTX concentrations have not been correlated with disease activity [5], a finding that is not surprising given that MTX has a short plasma half-life of elimination (~6 h) and is rapidly taken up into cells. RBC MTX polyglutamates have a long elimination half-life (weeks) [6] and are thus a potential candidate for monitoring MTX therapy. However, so far evidence does not strongly support a clinically useful relationship between MTX polyglutamate concentrations and disease activity or adverse effects in RA (Table 1).

There are a number of potential reasons for this lack of clear association. First, there are a number of variables that influence MTX polyglutamate concentrations, including dose, route of administration, duration of therapy, renal function, age, smoking status and concomitant medications [7, 8]. Second, it takes approximately 6 months for RBC MTX polyglutamate concentrations to reach a steady state [6] and the majority of studies have assessed the relationship with disease activity at earlier time points. Third, disease duration and the duration of MTX therapy may be important. While higher MTX polyglutamate concentrations are reported to be associated with lower disease activity in patients with early disease, this relationship may wane as the disease becomes established due to alterations in the biologic processes driving RA over time [9] and as resistance to therapy develops. Fourth, the cross-sectional design often employed for these studies leads to the potential for patients who tolerate and respond, even if only partially, to MTX to be overrepresented, with those patients intolerant to MTX or with no response underrepresented. Furthermore, the dose of MTX is often increased at 4- to 6-week intervals before steady state has been achieved, so there is the potential for some patients to receive a higher MTX dose than is actually required for adequate disease control. Finally, RBCs are not on the postulated causal inflammatory pathways nor are they purported to be involved in the mechanism of action of MTX. Thus they are only a surrogate marker for drug concentrations at the main site of action in disease control, i.e. synovium or inflammatory cells.

White blood cells (WBCs) have a critical role in driving the inflammatory process through their production of proinflammatory cytokines. Based on pharmacokinetic modelling studies, the kinetics of MTX polyglutamates in RBCs appear unlikely to reflect the intracellular MTX kinetics in WBCs [10]. This is consistent with a lack of correlation between RBC and peripheral blood mononuclear cell MTX polyglutamate concentrations in patients with JIA [11]. Whether the relationship between WBC MTX polyglutamate concentrations and disease activity is more reliable and clinically relevant remains to be determined.

**Current clinical role for measuring MTX polyglutamates**

The lack of a clear relationship between RBC MTX polyglutamates and disease activity or drug-related adverse effects limits their usefulness in TDM. The long half-life of RBC MTX polyglutamates also means they cannot be reliably used as a measure of compliance with drug therapy. The need for rapid inflammatory disease control means that clinicians need to be able to predict response after 4–6 weeks of MTX rather than waiting until steady-state
concentrations have been achieved. From a pragmatic clinical perspective, assessment of disease activity in RA is likely to inform changes in DMARD therapy rather than drug concentrations given these time constraints. Although this brings with it the risk of overtreatment, the step-down approach to therapy remains a rational approach. There may be a role for TDM if a clear relationship between the more severe adverse effects, such as bone marrow suppression and hepatotoxicity, and drug concentrations can be established. However, given that

RFC-1: reduced folate carrier; FPGS: folylpolyglutamate synthetase; GGH: γ-glutamyl hydrolase; TYMS: thymidylate synthase; ATIC: amino-imidazole carboxamidoribonucleotide (AICAR) transformylase; DHFR: dihydrofolate reductase; MTHFR: 5,10-methylenetetrahydrofolate reductase.

Fig. 1 MTX metabolism and mechanism of action.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Study design</th>
<th>Outcomes</th>
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<tr>
<td>Angelis-Stoforidis, 1999 [41]</td>
<td>65 RA patients on weekly MTX for at least 2 months</td>
<td>Cross-sectional study</td>
<td>MTX polyglutamate concentrations higher in responders compared with partial and non-responders ($P &lt; 0.001$). Polymorph MTX polyglutamate concentrations higher in responders compared with non-responders ($P = 0.0019$). No difference on mononuclear cell MTX polyglutamate concentrations between responders, partial responders or non-responders. No relationship between MTX polyglutamate concentrations and adverse effects.</td>
</tr>
<tr>
<td>Dervieux, 2004 [42]</td>
<td>108 RA patients on MTX for at least 3 months</td>
<td>Cross-sectional</td>
<td>Higher RBC MTXGlu$_3$ concentrations associated with lower SJC, TJC and physicians global assessment score. MTXGlu$_3 &gt; 60$ nmol/l associated with higher likelihood of physician assessed good response to MTX. Patients with a lesser decrease in DAS28 had lower RBC MTXGlu$_3$ concentrations. No relationship between MTX polyglutamate concentrations and adverse effects.</td>
</tr>
<tr>
<td>Dervieux, 2006 [43]</td>
<td>48 MTX-naive RA patients</td>
<td>Prospective longitudinal</td>
<td>Steady-state erythrocyte MTX concentrations significantly higher in responders compared with non-responders. RBC MTX polyglutamatcs significantly higher in patients with high disease activity. No association between RBC MTX polyglutamate concentrations and adverse effects. No association between RBC MTX polyglutamates and disease activity. Higher RBC MTXGlu$_{2,5}$ concentrations associated with abnormal liver function tests and gastrointestinal adverse effects. Significant correlation between RBC MTXGlu$_2$ and improvement in DAS28 over 16 weeks.</td>
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</table>
| Hornung, 2008 [44] | 76 RA patients with long-standing disease, 40/76 commencing MTX | Open-label prospective 52-week study | Erythrocyte MTX content measured and calculated as mean from week 6
Steady-state erythrocyte MTX concentrations significantly higher in responders compared with non-responders. |
| Stamp, 2010 [45] | 200 RA patients with long-standing disease on oral MTX for at least 1 month | Cross-sectional                   | High disease activity defined as DAS28 > 3.2 |
| Becker, 2011 [46] | 104 patients with JIA                         | Cross-sectional                   | Higher RBC MTXGlu$_{2,5}$ concentrations associated with abnormal liver function tests and gastrointestinal adverse effects. |
| Hobl, 2012 [47] | 19 MTX-naive RA patients                     | 16-week prospective open-label study | Significant correlation between RBC MTXGlu$_2$ and improvement in DAS28 over 16 weeks. |
these adverse effects are not common, this will require large, long-term studies of patients commencing MTX.

Anti-TNF therapy in RA

Biologic therapies have revolutionized the lives of many patients with rheumatic diseases. For patients with active early RA and poor prognostic features, TNF inhibitors are now recommended as first-line treatment [2]. However, as seen with most non-biologic DMARDs, there is considerable variation in the clinical response to treatment with anti-TNF therapy. In contrast to traditional DMARDs, biologic therapies, including anti-TNF therapy, are expensive, and more cost-effective use of these drugs would benefit both patients and health care systems. TDM for anti-TNF agents has received some attention recently. In IBD, there have been at least 20 studies with anti-TNF trough drug concentrations and/or anti-drug antibodies assessed in relation to disease activity and adverse effects. In a systematic review of these studies, it was concluded that there was a close relationship between trough drug concentrations and maintenance of response, with cut-off concentration values of between 3 and 7.2 μg/ml depending on the individual study [12]. It was also concluded that the presence of anti-TNF drug antibodies increased drug clearance. The authors suggest that TDM of anti-TNF drug concentrations and antibody titres may prove useful in IBD.

Relationship between anti-TNF drug concentrations and clinical response in RA

Small studies have been undertaken using three of the available anti-TNF therapies: etanercept (ETN), infliximab (IFX) and adalimumab (ADA). While it is too early to define therapeutic ranges, most of the studies to date suggest an inverse relationship between trough drug concentrations and response to therapy (Table 2).

One study used trough IFX concentrations to guide IFX dosing. In this small study of 24 RA patients, 6 patients had the dose of IFX increased because of inadequate disease control and low IFX trough concentrations (<8.0 μg/ml). The increase in IFX dose resulted in a mean decrease in the DAS28 of ~20% (P < 0.05). Furthermore, the decrease in the DAS28 correlated with an increase in serum IFX trough concentrations [13]. The authors concluded that TDM of serum IFX concentrations might improve disease control in patients with RA.

In a larger double-blind study, patients received IFX 3 mg/kg at weeks 0, 2, 6 and 14, then at week 22 the IFX dose was increased by 1.5 mg/kg if there had been insufficient response [reduction in tender joint count (TJC) and swollen joint count (SJC) <20% from baseline] or if there was subsequent deterioration (deterioration of at least 50%). Of the 329 patients, 100 (30.4%) required dose escalation and these patients tended to have lower trough IFX concentrations prior to the dose increase than those who did not require dose escalation [14].

The development of anti-drug antibodies has been associated with lower drug concentrations and poorer response to treatment in some studies [15–18]. However, Rahman et al. [14] reported no significant increase in the incidence of anti-IFX antibodies in those patients that required dose escalation, suggesting that low trough concentrations were a more important cause of inadequate response.

Current clinical perspective

Currently there are insufficient data to warrant routine measurement of anti-TNF drug concentrations or anti-drug antibodies in patients with inflammatory rheumatic diseases. However, given the cost of these agents, rational and targeted use is of importance, particularly given the limited health care budgets in many countries. It is already evident that the one-size-fits-all dosing approach is not appropriate for all patients. For example, the dose interval with ADA can vary from 10 to 14 days depending on response. It may be that in patients responding well the dose interval could be increased even further, an approach that could be guided by TDM. Conversely, in patients responding poorly, whether TDM can assist the clinician in deciding whether to increase the dose or change to an alternate therapy remains to be determined.

In a systematic review of 16 studies involving >8000 patients, 53.7% of the patients receiving IFX underwent dose escalation due to inadequate response [19]. The benefits of this approach are less clear. In a recent study of 141 RA patients with inadequate response to IFX, a dose increase from 3 to 5 mg/kg led to no significant improvement [20]. It may be that a more strategic approach to dose escalation could be provided by TDM, whereby only those patients with low drug concentrations might benefit from dose escalation, whereas patients with adequate drug concentrations would benefit from switching to an alternative agent. Well-designed prospective clinical trials will be required to ascertain whether such an approach is reasonable.

Allopurinol/oxypurinol monitoring in gout

While treatment targets in RA are based on more subjective outcome measures such as SJC and TJC, the treatment in gout is based on an objective outcome measure, namely SU. It is now well established that a sustained reduction of SU of <0.36 mmol/l, or lower (<0.30 mmol/l) if tophi are present, results in improved clinical outcomes [21]. Allopurinol is the most commonly used urate-lowering therapy. However, a number of patients fail to achieve the target SU concentration [22]. Potential reasons for poor response include non-compliance with therapy, underdosing of allopurinol [mainly due to adherence to creatinine clearance (CrCL)-based dosing protocols] and/or partial resistance to allopurinol (decreased conversion of allopurinol to oxypurinol or increased clearance of oxypurinol). True non-response to allopurinol appears to occur very rarely, if at all.

Allopurinol has a short half-life (~1–2 h) with the major route of elimination being through its metabolism to oxypurinol. In comparison, oxypurinol is eliminated primarily via the kidneys and thus its half-life is dependent on renal function. In those with normal renal function the half-life of oxypurinol is ~18–30 h, extending to a week in those with severely impaired renal function [23]. In patients with a CrCL <10 ml/min there is very little renal clearance of
### Table 2: Relationship between anti-TNF drug concentrations and disease activity in RA

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Drug concentration and disease activity</th>
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<tr>
<td><strong>IFX</strong></td>
<td></td>
<td>49% patients with IFX (\leq 1) mg/ml achieved (&lt;20%) ACR improvement compared with 29.5% patients with IFX (&gt;1) mg/ml.  [48]</td>
</tr>
<tr>
<td>St Clair, 2002</td>
<td>428 RA patients receiving IFX 3 mg/kg every 8 weeks, 3 mg/kg every 4 weeks, 10 mg/kg every 8 weeks or 10 mg/kg every 4 weeks.  Peak and trough IFX concentrations measured by ELISA with each infusion through 54 weeks.</td>
<td>11.7% patients with IFX (\leq 1) mg/ml achieved (&gt;70%) ACR improvement compared with 26.4% patients with IFX (&gt;1) mg/ml. Less radiographic progression in patients with higher trough concentrations (P &lt; 0.004).</td>
</tr>
<tr>
<td>Wolbink, 2005</td>
<td>105 RA patients receiving IFX 3 mg/kg. Trough IFX concentrations measured by ELISA at baseline and weeks 2, 4, 6 and 14. Non-response defined as a decrease in DAS28 after 14 weeks of (\leq 0.6) or a decrease (&gt;0.6) and (&lt;1.2) with an attained DAS of (&gt;5.1).</td>
<td>After 14 weeks responders had significantly higher trough serum IFX concentrations compared with non-responders (3.6) mg/l ((1.4-8.2)) vs (0.5) ((0.2-2.2), P &lt; 0.01).</td>
</tr>
<tr>
<td>Mulleman, 2009</td>
<td>24 RA patients treated with IFX.</td>
<td>Changes in DAS28 and trough serum IFX concentrations were inversely associated (P &lt; 0.02).</td>
</tr>
<tr>
<td>Mulleman, 2010</td>
<td>Cross-sectional study of 28 RA patients receiving IFX. Mean IFX dose 4.1 mg/kg (range 2.7-5.9 mg/kg). Trough IFX concentrations measured by EUSA.</td>
<td>IFX concentrations higher in patients with DAS28 (&lt;3.2) compared with those with DAS28 (&gt;3.2) ((3.26) mg/l vs (0.16) mg/l, (P &lt; 0.01)).</td>
</tr>
<tr>
<td>ADA</td>
<td></td>
<td>IFX concentrations (&gt;1.037) mg/l predicted DAS28 (&lt;3.2) with 84% sensitivity and 78% specificity.</td>
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<tr>
<td>Bartelds, 2007</td>
<td>121 RA patients treated with ADA 40 mg fortnightly. Disease activity and trough ADA concentrations assessed at baseline and weeks 4, 16 and 28.</td>
<td>EULAR non-responders had lower serum concentrations compared with EULAR good responders [median 5.4 mg/l ((0.0-21.2)) vs 9.8 mg/l ((0.0-33.0), P = 0.001)].</td>
</tr>
<tr>
<td>Bartelds, 2011</td>
<td>Prospective study of 272 RA patients treated with ADA 40 mg fortnightly. Disease activity, trough serum ADA concentrations and anti-ADA antibodies assessed at baseline and at eight time points to week 156.</td>
<td>No direct relationship between trough ADA and disease activity examined.</td>
</tr>
<tr>
<td>ETN</td>
<td></td>
<td>Patients without anti-ADA antibodies had higher serum ADA concentrations and were less likely to achieve low disease activity or clinical remission.</td>
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<tr>
<td>Jamnitski, 2012</td>
<td>Prospective study of 292 RA patients receiving ETN 25 mg s.c. twice weekly or 50 mg once weekly. DAS28 and trough serum ETN concentrations at baseline, 1, 4 and 6 months.</td>
<td>Serum ETN concentrations higher in EULAR good responders compared with EULAR moderate and poor responders at all time points.</td>
</tr>
<tr>
<td>Daien, 2012</td>
<td>18 female RA patients receiving ETN 50 mg s.c. weekly. DAS28 and trough serum ETN concentrations assessed at baseline, 3 and 6 months.</td>
<td>40% of non-responders had serum ETN (&lt;2.1) mg/l. 36% of all good responders had serum ETN (&gt;4.7) g/l. ETN concentrations at 3 months were lower in patients considered non-responders at 6 months compared with responders at 6 months ((1.75) (\mu)g/ml vs (3.7) (\mu)g/ml, (P = 0.03)). Best predictor of response at 6 months was ETN (&gt;3.1) (\mu)g/ml at 3 months.</td>
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oxypurinol [24]. Oxypurinol is responsible for most of the urate-lowering effect of allopurinol through inhibition of xanthine oxidase, the enzyme responsible for conversion of hypoxanthine to xanthine and xanthine to uric acid. This, combined with the long elimination half-life of oxypurinol, means that oxypurinol may be appropriate for TDM in gout.

**Relationship between oxypurinol and SU**

A plasma oxypurinol concentration of 100 μmol/l at 6–9 h post-allopurinol dosing has been suggested as the upper limit of the therapeutic range [25, 26]. However, the target SU for these studies was a normal SU, defined as <0.45 mmol/l, which is substantially higher than the current recommended target SU of <0.36 mmol/l. More recent data suggest that higher plasma oxypurinol concentrations (100–150 μmol/l) at 6–9 h post-dose are required to achieve the target SU of <0.36 mmol/l in the majority of patients [27].

The plasma oxypurinol concentration at 6–9 h post-dose has been used in previous studies examining the relationship between plasma oxypurinol and SU [25]. However, TDM traditionally uses trough concentrations, and it has been suggested that this may be more appropriate for oxypurinol as well. In one small study of 26 patients with gout and renal impairment (CrCL 25–60 ml/min) there was no significant difference between trough and 5-h post-dose peak oxypurinol concentrations [mean 23.46 (s.d. 13.7) μmol/l vs 31.77 (s.d. 14.3) μmol/l] [28]. Furthermore, while both trough and peak plasma oxypurinol concentrations correlated with the change in SU from baseline to week 6, the correlation was slightly stronger with trough measurements (trough $r^2 = 0.26$ vs peak $r^2 = 0.18$) [28]. Based on the oxypurinol half-life of elimination of ~23 h, the trough oxypurinol concentration is approximately two-thirds that at 6–9 h post-dose.

**Relationship between oxypurinol and adverse effects**

It has been suggested that high plasma oxypurinol concentrations are associated with AHS. This rare but potentially life-threatening syndrome is the most feared adverse event associated with allopurinol. However, this potential relationship is based on the observation that renal impairment is associated with both AHS and higher oxypurinol concentrations. There are only a handful of case reports of AHS where oxypurinol concentrations were actually measured [24, 29–31]. Interpretation of the data presented in these cases is hampered by variable times between the last allopurinol dose and the blood draw for oxypurinol. However, there is no clear evidence for increased plasma oxypurinol concentrations causing the AHS. Further evidence for the lack of association comes from studies that report high plasma oxypurinol concentrations in the absence of allopurinol-related adverse effects or AHS [27, 28].

**Current clinical role for measuring oxypurinol**

Plasma oxypurinol measurement may be most useful in those patients where SU fails to decline as expected with allopurinol therapy. In this setting, low plasma oxypurinol (<20 μmol/l) will help identify non-compliant patients so further efforts at educating the patient as to the importance of compliance can be undertaken. Whether TDM provides any clinical benefit in this setting is arguable, particularly when there is no association between elevated drug concentrations and adverse drug effects. Thus the pragmatic clinical approach is to ensure compliance and then continue to dose escalate allopurinol until the target SU is achieved, adverse effects occur or the maximum dose of 900 mg/day is reached irrespective of oxypurinol concentration. Further safety studies of allopurinol at doses above the CrCL-based dose are awaited.

**Colchicine**

Colchicine is used in the treatment of acute gout and for prophylaxis against gout when starting urate-lowering therapy. Colchicine is a highly lipophilic drug and is rapidly distributed throughout all tissues in the body. Peak plasma concentrations are achieved 1–2 h after oral administration of colchicine [32]. However, colchicine has a long half-life and can be detected in leucocytes 10 days after i.v. administration [33].

Colchicine has a narrow therapeutic index, with many patients experiencing dose-dependent gastrointestinal toxicity. Recently drug interactions between colchicine and CYP3A4 and P-glycoprotein inhibitors have been highlighted [34]. CYP3A4 is involved in the metabolism of colchicine to its inactive metabolites and co-administration of CYP3A4 inhibitors can result in colchicine accumulation and toxicity. P-glycoprotein (or ABCB1) is a drug transporter thought to limit gastrointestinal absorption of colchicine. P-glycoprotein inhibitors may therefore lead to the accumulation of colchicine. Indeed, co-administration of verapamil, a potent P-glycoprotein, and CYP3A4 inhibitor has been shown to increase plasma colchicine concentrations and reduces its clearance by ~50% [35].

There are currently no studies examining the role of TDM with colchicine in patients with gout. Plasma colchicine concentrations have been measured in some cases of fatal colchicine overdose with levels ranging from 10 to 250 ng/ml [36]. This wide concentration range suggests TDM may not be useful. From a clinical perspective, TDM is likely to be more useful when colchicine is being used in the long term for prophylaxis while starting urate therapy, particularly in patients receiving CYP3A4 or P-glycoprotein inhibitors, rather than short-term use for acute gout.

**Other DMARDs in rheumatic diseases**

**AZA**

The thiopurines AZA and 6-mercaptopurine are used in a variety of inflammatory diseases, including IBD, RA, connective tissue diseases and the vasculitides. In IBD, it has become common to use TDM by monitoring the concentrations of the thiopurine metabolites 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP). There is evidence for increased drug response with 6-TGN concentrations >235 pmol/8 x 10^8 RBCs [3]. Furthermore, 6-TGN concentrations >450 pmol/8 x 10^8
RBCs have been associated with an increased risk of myelotoxicity. Therefore a therapeutic range of 235–450 pmol/8 x 10⁶ RBCs is used. 6-MMP concentrations >5700 pmol/8 x 10⁶ RBCs have been associated with hepatotoxicity and dose regimens are altered so as not to exceed this threshold.

Despite the evidence in IBD, there is a paucity of data in inflammatory rheumatic disease. Only small studies of patients with inflammatory rheumatic diseases, including RA, SLE, myositis and polyarteritis nodosa, have been undertaken and no association has been observed between 6-TGN concentrations and hepatotoxicity or myelotoxicity or disease activity [37, 38]. These data suggest there is currently no role for the measurement of AZA or mercaptopurine metabolites, but this is somewhat surprising given the data in IBD. The apparent lack of utility of thiopurine metabolites in rheumatic diseases may reflect study design and low patient numbers. However, there is the potential for larger prospective studies to address this. HCQ

HCQ is used in both RA and SLE and is regarded as one of the least toxic and safest DMARDs. The most feared complication of HCQ is retinopathy. HCQ and its metabolites, which include desethyldydroxychloroquine, desethylchloroquine and di-desethylchloroquine, can all be measured. In patients with SLE it has been suggested that measurement of HCQ blood concentrations may improve management. In a study of 300 patients with discoid lupus, HCQ concentrations were significantly higher in those with complete remission compared with those with partial remission and/or treatment failure [39]. In a smaller study of patients with SLE, low whole blood HCQ concentrations were associated with higher disease activity and were a greater predictor of disease flare [40]. Larger studies will be required to confirm these findings and determine whether a therapeutic range can be identified.

Conclusions

There remains a need for technologies to optimize drug therapies to gain rapid, effective and safe control of inflammation in rheumatic diseases and prevent ongoing joint damage. TDM offers the potential to aid with this goal, and the monitoring of several drug therapies has been studied. The data to date suggest that the greatest potential is with the biologic therapies in RA, HCQ in SLE and to a lesser extent oxypurinol concentrations in gout. There may also be some potential with the thiopurine drugs in RA.

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Lisa K. Stamp and Murray Barclay


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