

Review

Biologic agents for rheumatoid arthritis—negotiating the NICE technology appraisals**Patrick D. W. Kiely¹, Chris Deighton², Josh Dixey³ and Andrew J. K. Östör⁴, on behalf of the British Society for Rheumatology Standards, Guidelines and Audit Working Group*****Abstract**

In England and Wales, the National Institute for Health and Clinical Excellence (NICE) has provided guidance [technology appraisals (TAs) 130, 186, 195, 198 and 225] on the use of biologic drugs for the treatment of RA. This is based on an analysis of efficacy, safety and cost-effectiveness, and has resulted in a complex management pathway that restricts freedom to prescribe biologics according to their licensed indications. Specifically, TNF antagonists are the only class of biologics that can be used first line in DMARD-inadequate responders, and only in patients with a persistent 28-joint DAS score of ≥ 5.1 . Alternative biologic agents are denied to those with contraindications to anti-TNF drugs and are also not supported following intolerance to TNF antagonists. Rituximab is the only class of biologic permitted after TNF antagonist inefficacy, in the absence of a contraindication to its use, whereas abatacept and tocilizumab are licensed and may be a more efficacious choice at this stage in some patient groups. Furthermore, for patients who demonstrate sequential inadequate responses, treatment is restricted to one TNF antagonist, rituximab and tocilizumab, whereas abatacept is only a permitted choice when rituximab is contraindicated or has been withdrawn because of an adverse event. In this review, we discuss the treatment algorithm published by NICE, and suggest alternatives where perceived deficiencies exist.

Key words: rheumatoid arthritis, biologic agents, guidelines, TNF antagonists, adalimumab, etanercept, certolizumab pegol, rituximab, abatacept, tocilizumab

Patients with RA and their physicians have been extremely fortunate over the last decade in having four classes of biologic agents licensed to combat the disease. This has led to a seismic shift in RA management resulting in disease remission, or at least low disease activity, as the therapeutic goal [1, 2]. However, in England and Wales the ability to deliver evidenced-based practice has been restricted by the National Institute for Health and Clinical Excellence (NICE) following the publication of five

technology appraisals (TAs 130, 186, 195, 198 and 225) providing guidance on the use of biologic drugs based on an analysis of efficacy, safety and cost-effectiveness [3–6]. The result is a complex management pathway that the majority of health commissioners in England and Wales insist rheumatologists follow (Fig. 1). Internationally, while not binding, these guidelines may also carry substantial influence. In this review we will attempt to navigate this algorithm and suggest alternatives where perceived deficiencies exist. Table 1 lists biologic agents according to licensed and NICE-approved status in different clinical scenarios.

Initial biologic therapy

The decision to initiate a biologic drug has been addressed by leading rheumatology societies worldwide (e.g. BSR, EULAR, ACR). A common consensus is that a biologic should be started in patients who fail to achieve a 28-joint DAS (DAS-28) < 3.2 after treatment with traditional DMARDs [7–11]. This contrasts with NICE TA 130

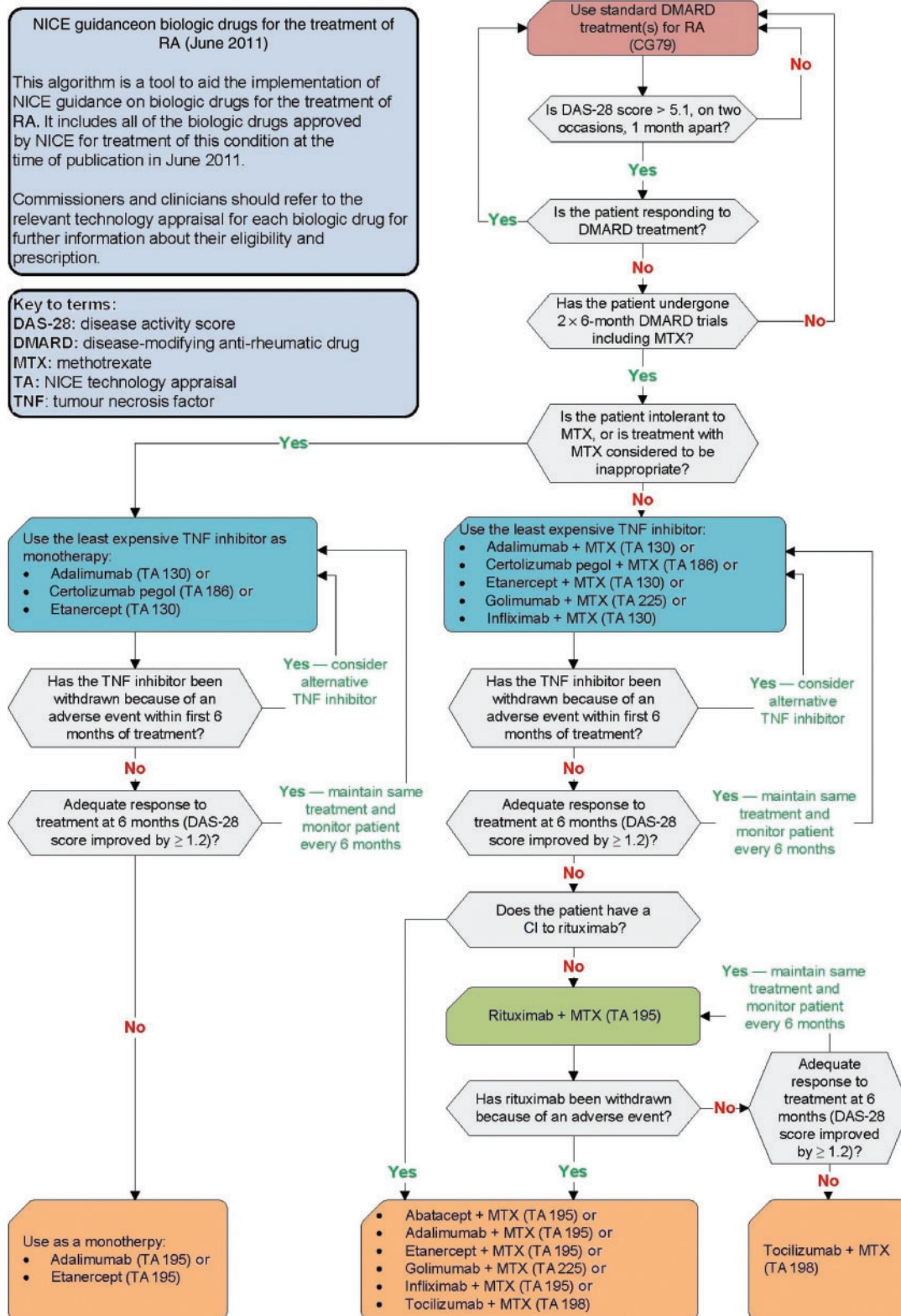
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*See supplementary data, available at *Rheumatology* online for the members of the British Society for Rheumatology Standards, Guidelines and Audit Working Group.

Fig. 1 Algorithm illustrating NICE guidance on biologic drugs for the treatment of RA. NICE (2011) algorithm: 'rheumatoid arthritis'. www.nice.org.uk. Reproduced with permission from NICE. Algorithm was accurate at the time of publication CI: contraindication.



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TABLE 1 Biologic agents for RA listed according to licensed and NICE-approved status in different clinical scenarios

Scenario	MTX tolerant		MTX intolerant	
	NICE approved	Licensed options	NICE approved	Licensed options
DMARD-IR	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, tocilizumab	Adalimumab, certolizumab pegol, etanercept	Adalimumab, certolizumab pegol, etanercept, tocilizumab
DMARD-IR, anti-TNF contraindication Anti-TNF intolerant	Alternative from adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab	Alternative from adalimumab, certolizumab pegol, etanercept	As DMARD-IR
Anti-TNF ineffective	Rituximab	As anti-TNF intolerant	Alternative from adalimumab, etanercept	As DMARD-IR
Anti-TNF ineffective, rituximab contraindication	Adalimumab, etanercept, infliximab, abatacept, tocilizumab	As DMARD-IR	Alternative from adalimumab, etanercept	As DMARD-IR
Rituximab intolerant	As anti-TNF ineffective, rituximab contraindication	As DMARD-IR	Not applicable	Not applicable
Rituximab ineffective	Tocilizumab	As DMARD-IR	Not applicable	Not applicable

(October 2007) that recommends anti-TNF therapies be started in patients who have a persistently elevated DAS-28 > 5.1, after failure of two DMARDs (including MTX, unless contraindicated) taken over a minimum time of 6 months each. This remains the current standard of practice in England and Wales, being at variance with many published guidelines and standards in the European Union and the USA, which emphasize the importance of not delaying the start of biologic therapy when required [1, 2]. The implication for patients with a DAS-28 between 3.2 and 5.1 is that improvement in disease activity may only be achieved by continuing traditional DMARDs and CSs. However, data from the Early Rheumatoid Arthritis Network, a prospective inception cohort of early RA in England and Wales, has shown that only 27% of patients with DAS-28 3.2–5.1 achieve a DAS-28 < 3.2 at Year 2 and 35% at Year 3 in routine care using conventional DMARDs [12]. Furthermore, this data set has also shown that patients with a DAS persistently in this range fair poorly, with sustained and substantial disability as documented by poor scores of function. For those living in England and Wales the time has surely come to pay greater attention to this patient group with a persistent DAS-28 of 3.2–5.1 despite conventional therapies, and permit the use of biologics in order to achieve remission, or at least low disease activity, according to current principles of best practice [1, 2, 11].

MTX intolerance

It is clear that outcomes are improved if TNF antagonists are co-prescribed with MTX [13, 14]. As such, NICE concurs with other guidelines that MTX remains the

cornerstone DMARD for RA. However, in routine care >30% of patients receive biologics as monotherapy [15, 16]. In those patients who are MTX intolerant, NICE allows the use of adalimumab, etanercept (TA 130) and certolizumab (TA 186) as monotherapy, in keeping with drug licences. In practice, clinicians may choose to co-prescribe an alternative DMARD to MTX, on the assumption that the benefit is not drug specific, but rather an effect of overall immunomodulation. An alternative first-line biologic may be tocilizumab, as this is licensed without MTX in DMARD-inadequate responder (IR) patients. There is randomized controlled trial (RCT) evidence for the use of tocilizumab as monotherapy [17] and in combination with non-MTX DMARDs [18]. Tocilizumab is therefore a legitimate choice as a first-line biologic in patients where MTX is not tolerated, but is not currently recommended under NICE guidelines.

Contraindications to TNF antagonists

Where contraindications to TNF antagonists exist, NICE provides no alternative first-line biologic option. The summary of product characteristics (SmPC) for anti-TNF drugs list active tuberculosis or other severe infection including sepsis or risk of sepsis, active infection including chronic or localized infection, and opportunistic infection, as well as moderate to severe heart failure [New York Heart Association (NYHA) Class III/IV] as contraindications to their use. Clinicians must also balance the risk/benefit of a range of other conditions listed as precautions to the use of TNF antagonists, such as history of malignancy, blood dyscrasias, demyelinating disease, chronic obstructive pulmonary disease, vasculitis, as well as viral

and alcoholic hepatitis. These disorders are sufficiently common that a significant proportion of patients will either be excluded from receiving TNF antagonists, or treated with trepidation. In this situation, an alternative biologic should be available, as risk/benefit analysis may confer a preference over anti-TNF drugs. Both abatacept and tocilizumab are licensed for first-line biologic use (rituximab is not) on the basis of trial evidence in DMARD-IR patients [19–21]. They may therefore be legitimately considered as alternative first-line biologics, especially where relative and absolute contraindications to TNF antagonists exist. At present this is not recommended under NICE guidelines.

Intolerance to first TNF antagonist within 6 months

In this situation, NICE (TAs 130 and 186) allows a switch within anti-TNF class. However, NICE provides no guidance for patients who have responded but develop an adverse event after the first 6 months of therapy. These patients should also be allowed to switch to an alternative TNF antagonist. Furthermore, there is no guidance if the patient is also intolerant to the second or third anti-TNF agent. Arguably these patients are effectively at the first biologic stage, because intolerance has denied them the opportunity of a therapeutic response to TNF antagonists. Evidence exists that such patients may respond to a different class of biologic, including abatacept, rituximab and tocilizumab. Abatacept and tocilizumab are licensed in DMARD and anti-TNF-IR patients, and rituximab is licensed for patients who have been intolerant to one or more TNF antagonists. Therefore, they may all be used legitimately at this juncture. Of these, tocilizumab can be given as monotherapy in MTX-intolerant patients. Nevertheless, none of these options are currently recommended by NICE guidelines.

Poor efficacy of first anti-TNF drug in MTX-intolerant patients

In this situation, NICE (TA 195) supports a within-class switch to either adalimumab or etanercept monotherapy. Certolizumab is not covered by TA 195, but would be an acceptable alternative. Thus there is then no guidance if these too are ineffective. Although NICE allows a switch to another biologic class in this situation in MTX-tolerant patients (TAs 195 and 198), there is no allowance for MTX-intolerant patients. A legitimate alternative would be tocilizumab, which is licensed for monotherapeutic use in MTX-intolerant patients and has proven efficacy in anti-TNF-IR patients; however, in the key TNF-IR trial, all patients were co-prescribed MTX [22].

Poor efficacy of first anti-TNF drug in MTX-tolerant patients

NICE (TA 195) supports rituximab alone as the second-line biologic option, assuming no contraindications exist to its

use. This is a logical and appropriate course, especially for patients who are seropositive for RF and/or anti-citrullinated protein antibodies ACPAs. However, rituximab is not unique among the biologics in working well in this cohort. In contrast, EULAR guidelines recommend a choice at this stage between all classes of licensed biologics [10], which allows clinicians freedom to use biomarker and other characteristics to individualize therapy. Rituximab has proven efficacy in anti-TNF-IR patients [23]; however, some uncertainty exists over future treatment options if hypogammaglobulinaemia develops following repeat cycles. As such, guidance to use rituximab as the only second-line biologic is constrictive, outside the approach adopted by EULAR, and likely to lead to certain patients not being treated with the most appropriate class of biologic at this stage. This is especially true of those patients who are both RF and ACPA negative, where the evidence (mainly from MTX-IR RCTs) suggests that this group does not benefit as much as those patients who possess these antibodies [23–25].

Poor efficacy of first anti-TNF drug in MTX-tolerant patients where rituximab is contraindicated

NICE allows a switch within the anti-TNF class or the use of abatacept (TA 195) or tocilizumab (TA 198). NICE TA 195 refers to the rituximab SmPC for definitions that would contraindicate its use, these being active, severe infection, the severely immunocompromised and those with severe heart failure (NYHA Class IV) or severe uncontrolled cardiac disease. As previously mentioned, in clinical practice there is hesitancy to prescribe rituximab to antibody-negative patients, given the lower likelihood of clinical benefit [23–25]. Thus seronegativity for RF should allow access to another biologic class with a potentially higher likelihood of response. NICE provides no guidance regarding therapeutic options if the first-choice second-line biologic agent is ineffective or not tolerated. There is no reason to assume, however, that a further switch between classes would not yield benefit in the rituximab-contraindicated population.

Intolerance to rituximab

NICE allows switching to an alternative anti-TNF (TA 195) or abatacept (TA 195) or tocilizumab (TA 198) if rituximab is not tolerated, but gives no further guidance if this next option is not tolerated or ineffective. There is no evidence to suggest that a further between-class switch (fourth-line biologic) would be ineffective or not tolerated. The treatment alternatives at this stage are limited and patients in this situation should have an opportunity to receive a trial of all licensed biologics, particularly as our current ability to match a biologic with an individual cannot exclude the chance of response.

TABLE 2 Biologic agent comparisons, incidence of serious infections

Biologic drug	Speed of onset	Half-life	Incidence of serious infections	Contraindicated in heart failure
Adalimumab	Fast	14 (10–20) days	4.3 per 100 patient-years vs 3.0 per 100 patient-years in placebo and active control-treated patients	Yes ^a
Certolizumab pegol	Fast	14 days	6.0 per 100 patient-years vs 2.0 per 100 patient-years placebo	Yes ^a
Etanercept	Fast	4 days (70–132 hours)	6.3% of RA patients treated for up to 48 months	No ^b
Golimumab	Fast	9–15 days	5 per 100 patient-years vs 6 per 100 patient-years for control patients (1 year data)	Yes ^a
Infliximab	Fast	8–9.5 days	Data not quoted in SmPC	Yes ^a
Rituximab	Slow	20.8 (8.5–35.9) days	Approximately 4 per 100 patient-years	Yes ^c
Abatacept	Slow	13 (8–25) days	2.87 per 100 patient-years; 1.8% vs 1.0% of placebo-treated	No
Tocilizumab (8 mg/kg)	Fast	13 days	5.3 per 100 patient-years vs 3.9 per 100 patient-years in placebo + DMARD group	No

Source: SmPC. ^aNYHA Grade III and IV; ^bnot contraindicated but SmPC advises caution; ^cNYHA Grade IV.

Rituximab inefficacy

Despite the absolute absence of evidence, NICE supports a switch to tocilizumab alone if rituximab is inefficacious (TA 198). This contrasts with the rituximab-intolerant population, where a second anti-TNF agent or abatacept are also allowed. This is inconsistent guidance, and the choice of either a switch back to a second TNF antagonist or abatacept or tocilizumab should be permitted for rituximab-IR patients.

At present, if a patient is MTX tolerant but fails to respond to each biologic in turn (with no contraindications or intolerance), the NICE algorithm (Fig. 1) sequences anti-TNF followed by rituximab and then tocilizumab, with no option to use abatacept, or to switch within anti-TNF class. This guidance, if adhered to, is contrary to the evidence base [26, 27], and will deny patients all options to achieve a state of low disease activity or remission.

For patients who develop intolerance to biologics, the NICE algorithm (Fig. 1) is also inconsistent. At the anti-TNF stage the patient cannot move to another class of biologic, despite both abatacept and tocilizumab being licensed for DMARD-IR patients with good evidence for efficacy [19–21]. At the rituximab stage a patient can progress to abatacept or tocilizumab if intolerant, yet may only be treated with tocilizumab if rituximab is ineffective. These are anomalies that are not supported by data and prevent the use of the right drug at the right time.

Individualizing biologic therapy

Treatment algorithms as well as cost-effectiveness will be transformed by the ability to match an individual patient to a biologic, based on the mode of action and likely tolerability. The risk of infection is particularly important, as all classes are associated with increased risk, with differences in half-life governing the speed of elimination. The

rates of serious infections quoted in the SmPC for each biologic agent are shown in Table 2. The following highlights the benefits and drawbacks of abatacept, rituximab and tocilizumab as therapeutic options in relation to TNF antagonists.

Abatacept

There is extensive RCT evidence for efficacy of abatacept in MTX-IR and TNF-IR RA patients, including those seropositive and seronegative for RF, and it is licensed in combination with MTX in both MTX-IR and TNF-IR patients [20, 21, 26, 28]. Infusion reactions are rare, and the onset of action is slower than TNF antagonists, but incremental benefit is reported beyond 1 year of treatment. As with all biologics, abatacept is contraindicated in severe and uncontrolled infection. The rate of serious infections quoted in the SmPC is modest (Table 2) and consistent with expectations based on RA cohorts treated with conventional DMARDs. This may relate to mode of action, as abatacept modulates T-cell co-stimulation without depleting or completely inhibiting T cells. Thus, for patients with an increased risk of sepsis, the benefit/risk profile of abatacept appears to be favourable, with the possible exception of those aged >65 years, where the incidence of serious infection is reported to be higher than those <65 years (SmPC). Reassuringly in RCTs, no increased autoantibody- cardiovascular- or malignancy-related adverse events over that expected in an RA population are reported, and abatacept is not contraindicated in patients with heart failure.

Rituximab

There is extensive RCT evidence for efficacy of rituximab in MTX-IR and TNF-IR RA patients [23, 29], although it is only licensed in TNF-IR patients in combination with MTX. Rituximab appears particularly suited to patients

with B-cell-driven disease, including autoantibody positivity (RF, ACPA, ANA), hypergammaglobulinaemia, nodules and features of secondary SS. Rituximab is contraindicated in patients with NYHA Class IV heart failure or severe uncontrolled cardiac disease, and evidence suggests that it is less suited to seronegative patients [23–25]. The duration of each rituximab infusion and high frequency of infusion-related reactions, including a cytokine release syndrome accompanied by hypotension and bronchospasm in 10% of the patients, places particular responsibility on clinicians. The rate of serious infection quoted in the SmPC is similar to TNF antagonists (Table 2). Hypogammaglobulinaemia is an unknown concern with respect to the safety of rituximab in the long term or after switching to another biologic agent or traditional DMARD. Similarly, long-term B-cell depletion, in some patients lasting for years, is of unknown consequence for the patient and the safety of future therapies. The inability to predict or reverse B-cell depletion provides some hesitancy to commit a patient to rituximab, especially when the other biologic classes may be used with similar efficacy and greater flexibility in the face of toxicity, including shorter half-life.

Tocilizumab

There is extensive RCT evidence for the efficacy of tocilizumab in MTX-IR and TNF-IR RA patients, including those seropositive and seronegative for RF and as a monotherapeutic agent [17–19, 22]. Tocilizumab is licensed in both MTX-IR and TNF-IR patients, may be used without MTX, and the onset of action is similar to TNF antagonists. Tocilizumab appears particularly suited to patients with features of IL-6-driven disease, including high CRP, anaemia of chronic disease, systemic involvement and fatigue. The rate of serious infection quoted in the SmPC and recent meta-analysis is similar to TNF antagonists (Table 2) [30]. However, inhibition of CRP and neutropenia in some patients (3.4%) requires vigilance, as signs and symptoms of sepsis may be diminished. Gastrointestinal perforation in the presence of diverticular disease has been reported, and tocilizumab should be used with particular caution in these patients. Thus the benefit/risk profile of tocilizumab with respect to infection does not appear to be any more favourable than TNF antagonists. Reassuringly, in RCTs no increased autoantibody, cardiovascular- or malignancy-related adverse events have been reported, and tocilizumab is not contraindicated in patients with heart failure. Regular monitoring of lipids, hepatic enzymes, neutrophils and platelets is required, and this may influence the benefit/risk analysis in some patients.

In conclusion, the optimal sequencing of biologic agents is currently unknown. Until patient profiling with robust biomarkers becomes available, treatment decisions remain guided by the licensed indications and the extensive evidence base of efficacy in varied situations. This must be balanced with the likely risk of toxicity with each class of biologic. The current NICE TAs restrict this process, not least in preventing the use of biologics in

patients with a DAS-28 above a minimal acceptable target of 3.2 but <5.1, and in constraining choices particularly for MTX-intolerant patients (anti-TNF agents only) or serial IR patients (no switching within anti-TNF class or use of abatacept). This review provides an analysis of the situations where alternatives arise and has suggested a legitimate course of action in each case. Our goal as rheumatologists remains one of achieving remission in all RA patients in order to maximize physical, psychological, and economic outcomes.

Rheumatology key messages

- Biologic agents are denied to those with contraindications to anti-TNF drugs.
- Alternative biologics are not supported following intolerance to anti-TNF agents.
- Sequential IR restricts treatment to one anti-TNF agent, rituximab and tocilizumab.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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