Guidelines

The 2013 BSR and BHPR guideline for the use of intravenous tocilizumab in the treatment of adult patients with rheumatoid arthritis

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Background

RA is a chronic multisystem inflammatory disorder with a prevalence of 0.5–1% in the general population. The management of RA has evolved considerably in the last few decades and newer therapies continue to be developed. Tocilizumab (TCZ) [1] is a humanized anti-IL-6 receptor (anti-IL-6R) antibody licensed for use in combination with MTX for the treatment of moderate to severe RA in adult patients who have either responded inadequately to or who were intolerant to previous therapy with one or more DMARDs or TNF antagonists. In such patients, TCZ can be administered as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Several large randomized controlled trials (RCTs) have demonstrated the efficacy and tolerability of TCZ in the treatment of RA.

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Why do we need this guideline?

A number of systematic literature reviews assessing both the efficacy and safety of TCZ in RA have been published in the last few years. In 2010 a Cochrane review [2] analysed the efficacy and safety of TCZ. The National Institute for Health and Care Excellence (NICE) produced guidelines for the use of TCZ in 2011 [3] and these were reviewed in 2012 [4]. Recently the European League Against Rheumatism (EULAR) published a consensus statement on the use of TCZ across all indications [5, 6]. Despite these extensive reviews, specific guidance on the use of TCZ for RA in the context of clinical practice in the UK and a pragmatic approach to the monitoring and management of its adverse effects was felt to be lacking.

Objective

The objective of this guideline produced under the auspices of the Standards Audit and Guidelines Working Group (SAGWG) of the British Society for Rheumatology (BSR) (guidelines protocol May 2012) is to provide evidence-based recommendations for the safe and effective use of TCZ in adult patients with RA.

Target population

The target population for this guideline is adult patients (≥18 years of age) with RA. Although the studies included in this guideline recruited patients based on the 1987 ACR classification criteria, the guideline should also apply to patients that meet the 2010 ACR/EULAR classification criteria for the diagnosis of RA. These guidelines specifically exclude paediatric patients. The guidelines are not restricted to any ethnic group, although, where available, data on ethnicity were collected to evaluate external validity and generalizability of the individual studies.

Areas not covered by the guideline

The guideline does not cover the use of TCZ in paediatric patients or indications other than RA. In addition, the guideline does not cover the use of s.c. TCZ.

Target audience

The guideline is primarily targeted towards rheumatologists, rheumatology nurses/allied health professionals and rheumatology specialty registrars directly involved in the management of RA in the UK. The guideline may also be useful to other secondary care physicians and general practitioners who may have patients under their care with RA who are receiving TCZ.

Stakeholder involvement

The guidelines working group consisted of rheumatologists from a range of clinical backgrounds, allied health professionals and a lay member from a patient representative organization. Working group members contributed to the processes for agreeing the key questions, the guideline content and the key recommendations.

Rigour of development

Statement of scope of the literature search and strategy employed

The BSR guidelines protocol (latest version May 2012) was used in the development of this guideline. Having reviewed the most recent NICE guidelines and other systematic reviews (including the Cochrane review) on the use of TCZ in RA, members of the working group were asked to identify specific areas that had not been covered elsewhere or had arisen from very recently presented data. Based on these identified areas, a list of specific research questions was formulated. This was circulated to the members of the working group and, following a consensus, a final list of key questions was produced using the Scottish Intercollegiate Guidelines Network (SIGN) methodology and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and based on the Patient, Intervention, Control, Outcome and Time-frame (PICOT) model [7].

The following key questions were identified:

In adult patients with moderate to severe RA:

(i) Is TCZ monotherapy effective in reducing the signs and symptoms of RA in patients intolerant to MTX?
(ii) What is the effect of TCZ therapy on the lipid profile and how should this be monitored and treated?
(iii) What is the effect of TCZ on neutrophil count and how should this be monitored and treated?
(iv) What is the effect of TCZ on liver function and how should this be monitored?
(v) Is TCZ therapy associated with increased risk of post-operative infection and how should the dosing regimen be modified in patients undergoing elective surgery?
(vi) Is TCZ safe for use during pregnancy and breastfeeding?
(vii) Is vaccination safe and effective in patients on TCZ?
(viii) Does the use of TCZ increase the risk of gastro-intestinal (GI) perforation?

In an attempt not to duplicate work already published, the following areas were excluded from this guideline:

(i) The efficacy of TCZ in combination with MTX.
(ii) The risk of major adverse events such as serious infection and malignancy.

The working group felt that these areas had been adequately covered elsewhere (2–6) and review of these data at this point in time would not be of further value.

Search strategy

Two members of the working group (A.P.M., A.J.K.O.) identified a list of keywords separately. A systematic literature search of the MEDLINE, EMBASE and Cochrane databases was performed from the inception of the databases to November 2011 to identify all relevant research papers. A second search was carried out in December 2012 to capture newer publications since the previous

TABLE 1 MEDLINE/EMBASE search strategy

No	Search criteria
1	exp ARTHRITIS, RHEUMATOID/
2	rheumatoid arthritis.af
3	((rheumatoid or rheumatoid or revmatoid or rheumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or disease$ or condition$ or nodule$)).af
4	(felty* adj2 syndrome).af
5	(caplan* adj2 syndrome).af
6	(sicca adj2 syndrome).af
7	still* disease.af
8	bechterew* disease.af
9	1 OR 2 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
10	exp RECEPTORS, INTERLEUKIN-6/
11	exp INTERLEUKIN-6/
12	Tocilizum*.af
13	Atlizumab.af
14	Atlizum*.af
15	actemra.af
16	IL-6.af
17	anti-IL-6.af
18	anti*IL*6.af
19	anti-interleukin-6.af
20	interleukin-6.af
21	11 OR 12 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
22	10 AND 23

search. The search strategy used is outlined in Table 1. In addition, the clinicaltrials.gov database was interrogated to identify relevant trials and ongoing studies.

Criteria for study inclusion

RCTs, case–control studies, observational (cohort) studies and case series were included in the initial search. Descriptive reviews, qualitative research studies and non-English-language publications were excluded. A separate search of the Web of Science was conducted to identify relevant conference abstracts. These were only included when no other source of data was available.

Extraction of data

A title and abstract review was carried out by A.P.M. on the search results and papers that met the aforementioned criteria were then loaded onto a Web browser-based reference management software (Zotero) and duplicates removed. Full-text versions of relevant papers were then obtained. Fig. 1 highlights the search and selection process.

Data analysis

Evidence tables were generated for each research question. For the purpose of efficacy analysis, only RCTs were included. Based on SIGN methodological principles, each paper was critically appraised for internal as well as external validity and a level of evidence assigned as per SIGN criteria [7]. Recommendations were made based

on the available evidence and the strength of the recommendation was assigned accordingly. Data derived from conference abstracts could not be evaluated with the same robustness, so any recommendation that relied wholly on such abstracts was graded D. Members of the working group were then asked to allocate a score (0–10) for each recommendation, indicating their level of agreement. A working group consensus score for each recommendation was then calculated as the average of these scores.
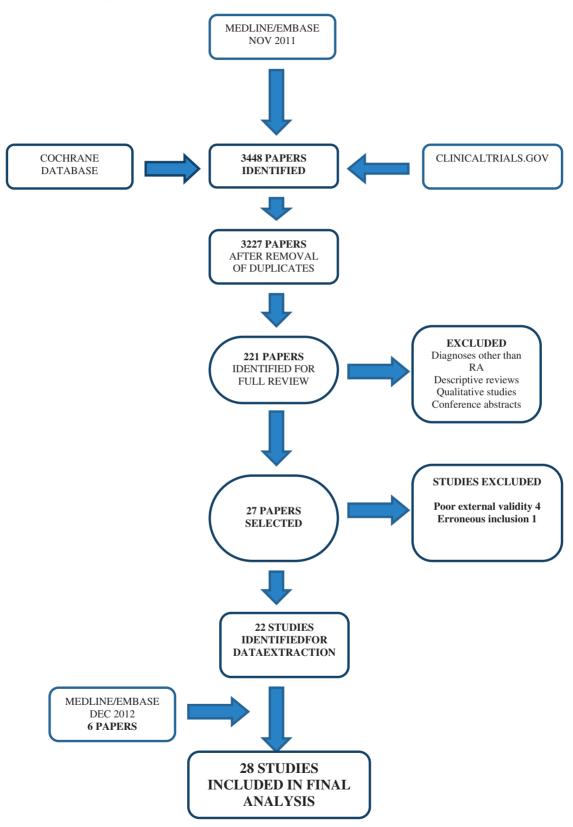
The guideline

TCZ monotherapy

In adult patients with moderate to severe RA intolerant to MTX, is TCZ monotherapy effective in reducing signs and symptoms of the disease?

In a phase II multicentre double-blind placebo-controlled RCT conducted in Japan [8], patients with refractory RA were randomized to receive TCZ 8 mg/kg, TCZ 4 mg/kg or placebo. The median duration of RA was 7.6 years and patients had received a median of four to five previous DMARDs. The ACR20 [9] response (a 20% improvement in ACR criteria) at 12 weeks was 78%, compared with 11% in the placebo group ($P < 0.001$). The SATORI study [10] was a double-blind active control study comparing the efficacy of TCZ monotherapy with MTX monotherapy in patients with an inadequate response to MTX. At 24 weeks, 80% of patients in the TCZ arm achieved an ACR20 response, compared with 25% in the MTX arm ($P < 0.001$). A 28-joint DAS (DAS28) remission was seen in 43% of patients in the TCZ arm *vs* 1.6% in the MTX arm. In the STREAM open-label extension study [11] conducted in Japan looking at the safety and efficacy of TCZ monotherapy in patients with RA refractory to conventional DMARDs, ACR20/50/70 response rates were maintained at 84%, 69% and 44%, respectively, at 5 years. Although these studies clearly indicate that TCZ monotherapy is effective, they were all limited to Japanese patients and extrapolation of these data to a predominantly Caucasian population in the UK may not be appropriate. Moreover, the dose of MTX used routinely in Japanese patients is much lower than that used in the UK (the median dose of MTX in the SATORI study was 8 mg/week).

The CHARISMA study (randomized double-blind parallel-arm study) [12] compared the efficacy of different doses of TCZ (2, 4 and 8 mg/kg) with or without MTX over a period of 16 weeks. The primary endpoint ACR20 response was achieved in 63% of patients on TCZ monotherapy, compared with 41% of patients on placebo and MTX ($P < 0.05$). No statistically significant difference was seen between these two groups in the ACR50 and ACR70 responses. In comparison, the ACR20 response in the group receiving TCZ and MTX was 74%, and although the study was not powered to look at this, it suggests that although TCZ monotherapy may have an advantage over MTX monotherapy, it may still be inferior to combination therapy with MTX. In the AMBITION study (an RCT

Fig. 1 Flowchart outlining the literature search with timelines


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                                   │                     │  Qualitative studies │
                                   │                     │  Conference abstracts│
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                        ┌──────────────────────┐        ┌──────────────────────┐
                        │  27 PAPERS           │        │  STUDIES EXCLUDED    │
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│ MEDLINE/     │                   │
│ EMBASE       │ ─────►            ▼
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comparing TCZ monotherapy with MTX monotherapy in patients with moderate to severe RA) [13], in the intention-to-treat group an ACR20/50/70 response was seen in 70%, 44% and 28% of patients in the TCZ arm compared with 53%, 34% and 15% of patients in the MTX arm, respectively ($P < 0.001$). However, only 66% of patients recruited into this study were MTX naive and >40% of patients had a disease duration of <2 years. In 2010 Singh *et al*. [2] published the results of a Cochrane systematic review of the use of TCZ in the treatment of RA. Based on their analysis, the authors concluded that patients on TCZ monotherapy are 21 times more likely to achieve an ACR50 response compared with placebo and 2.76 times more likely to achieve an ACR50 response compared with patients on MTX alone.

Data from the ACT-RAY study have been published recently [14]. In this study, patients with an inadequate response on an established dose of MTX were randomized to receive i.v. TCZ 8 mg/kg (combination therapy arm) or to receive TCZ monotherapy (MTX replaced with placebo). This study achieved its primary endpoint, i.e. no statistically significant difference in the DAS28 ESR remission rates between the two groups at 24 weeks (40% in the combination arm, 35% in the monotherapy arm; $P = 0.19$). There was, however, a numerical superiority in the combination arm for most outcomes that did not achieve statistical significance at 24 weeks.

Recommendations

(i) In moderate to severe RA, i.v. TCZ at a dose of 8 mg/kg reduces the signs and symptoms of disease and may be used as monotherapy if the patient is deemed intolerant to MTX (level of evidence 1+, grade of recommendation B, working group consensus score 9.9/10).

(ii) In patients with an inadequate response to MTX but no tolerability issue, it is recommended that therapy with MTX be continued (level of evidence 1+, grade of recommendation B, working group consensus score 9.9/10).

Safety considerations

What is the effect of TCZ therapy on the lipid profile and how should this be monitored and treated?
There has been considerable debate on the effects of TCZ on lipid profile and the implications for cardiovascular morbidity and mortality. Chronic inflammatory diseases such as RA are associated with high circulating levels of IL-6, which in turn is associated with lower cholesterol levels. The exact cause for this is uncertain, but an activated reticulo-endothelial system is believed to be, at least in part, responsible [15]. Suppression of the downstream effects of IL-6 by TCZ may reverse this effect. In addition, IL-6R signalling is also directly implicated in atherogenesis. A Mendelian randomization analysis interrogating a variant of IL-6R (Asp358Ala) with reduced IL-6R signalling found that in addition to dampened inflammation, every copy inherited was associated with a 3.4% reduced risk of coronary heart disease [16].

In a small, unpublished study of the effect of TCZ on markers of atherogenic risk in patients with RA [17], patients were randomized to receive either TCZ and MTX or placebo and MTX for 24 weeks (results on clinicaltrials.gov). The primary endpoint was a change in the number of small low-density lipoprotein (LDL) particles (as measured by nuclear MRI) and a change in aortic pulse wave velocity. No statistically significant difference was seen in either group over 24 weeks.

The use of TCZ in patients with moderate to severe RA is associated with an increase in serum total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides [12, 18, 19]. The use of anti-TNF agents has also been shown to increase total cholesterol and HDL cholesterol, and in a meta-analysis a maximum increase of 10% in total cholesterol and 7% in HDL cholesterol was seen [20].

In most published RCTs, lipid levels stabilize after the initial few months of treatment with TCZ [11, 12, 17, 18]. Despite the higher LDL cholesterol, the net effect on the atherogenic index (total cholesterol/HDL cholesterol) is neutral. This has been confirmed in long-term extension studies [11]. Its impact on cardiovascular morbidity, however, is currently unknown. TCZ use in RCTs and their long-term extensions have not demonstrated an excess of cardiovascular disease thus far [11], however, it may be too early for a signal to be evident. A study is currently under way to address this question [21].

There is some evidence that in chronic inflammatory states such as RA, IL-6 inhibits the cytochrome P450 enzyme system in the liver [22]. Simvastatin is metabolized in the liver by cytochrome P450 enzymes. In a small experimental study in RA patients, the use of a single dose of TCZ 10 mg/kg was shown to reduce the bioavailability of simvastatin to half of its pre-TCZ level [22]. The clinical significance of this is currently unknown, but it highlights the need for regular monitoring of lipids in patients established on statins.

Recommendations

(i) All patients commencing TCZ should have a baseline fasting lipid profile and, if abnormal, be treated in accordance with local guidelines (level of evidence 2++, strength of recommendation B, working group consensus score 9.7/10).

(ii) All patients should have a repeat fasting lipid profile in 3 months and treatment instituted/altered if appropriate (level of evidence 2++, strength of recommendation B, working group consensus score 9.7/10). Further monitoring should be guided by local practice and the existence of other risk factors.

In patients with RA, what is the effect of TCZ on neutrophil count and how should this be monitored and treated?

There is compelling clinical trial evidence that the use of TCZ at a dose of 8 mg/kg is associated with a significant decrease in the absolute neutrophil count (ANC), and the

summary of product characteristics (SPC) does not recommend the initiation of TCZ in patients with a pre-treatment ANC $<2 \times 10^9$/l [1].

The TCZ SPC recommends the following dose adjustments for patients on treatment:

When the ANC is $>1 \times 10^9$/l on TCZ, no change to the dose of TCZ is necessary. For an ANC of $0.5-1 \times 10^9$/l it is recommended that TCZ therapy be interrupted until levels are $>1 \times 10^9$/l. Therapy is to be restarted at 4 mg/kg and then increased to 8 mg/kg if clinically appropriate. In patients with an ANC $<0.5 \times 10^9$/l, TCZ is to be discontinued.

In clinical trials, this decrease in the ANC has not been found to be temporally associated with sepsis. Various hypotheses have been proposed for TCZ-associated neutropenia. The lower neutrophil counts have been attributed to peripheral margination, although this has not been proved [23]. In a recent paper, Nakamura *et al.* [23] reported that the ANC decreased significantly within 24 h of TCZ infusion and then completely recovered within 4 weeks.

In clinical trials, Common Terminology Criteria (CT) grade 3 (ANC $0.5-1 \times 10^9$/l) and grade 4 (ANC $<0.5 \times 10^9$/l) have been reported to occur in 2.9–6.3% of patients. The rates of grade 1 (ANC $1.5-2 \times 10^9$/l) and 2 (ANC $1-1.5 \times 10^9$/l) neutropenia are significantly higher. In a meta-analysis of six trials and five long-term extensions with a median duration of exposure of 3.6 years, Nishimoto *et al.* [24] found that the occurrence of grade 3/4 neutropenia at least once during the study was seen in ~6% of patients. Grade 1/2 neutropenia was seen in 15% of patients. In this meta-analysis, the authors found no association between low ANC and neutropenic sepsis [24]. In the CHARISMA study, a saw-tooth pattern of neutrophil counts was noted, levels reaching a nadir midway between 4-week infusions [12]. In patients with neutropenia, the ANC tended to recover after cessation of the drug.

According to the TCZ SPC, ~50% of cases of CTC grade 3/4 neutropenia were reported within the first 8 weeks of therapy. In a cumulative analysis of safety data that included 4009 patients exposed to TCZ [19], the mean baseline ANC was found to be 5.82×10^9/l. This dropped to 3.85 at week 2 (post-dose) and then remained stable at 4.61 and 4.07×10^9/l at 4 weeks and 24 weeks, respectively. Only one case of sepsis (empyema) associated with grade 3 neutropenia was reported in this analysis.

Recommendations

(i) As patients on TCZ are at risk of neutropenia, we recommend 4-week monitoring of the ANC for the first 6 months. If significant neutropenia (grade 3/4) does not occur during this period, monitoring can be performed less frequently and be guided by other concomitant DMARDs (level of evidence 2+, grade of recommendation D, working group consensus score 9.6/10).

(ii) For monitoring purposes, the full blood count should be checked in the week leading up to the next infusion (level of evidence 3, grade of recommendation D, working group consensus score 9.6/10).

Good practice point: Although there appears to be little correlation between neutropenia and sepsis in the clinical trials, we strongly recommend that patients and their general practitioners be counselled regarding neutropenia. It would also be good practice that the full blood count be checked promptly if patients develop fever, with appropriate treatment initiated if grade 3/4 neutropenia is identified.

Please note that the grade of recommendation for this section is D, which indicates that the recommendation is based on the opinion of the working group. The evidence indicates that although significant neutropenia is most likely to occur in the first 8 weeks, it is also reported in the extension studies. It is unclear from the data whether the neutropenia reported from the extension studies reflects tests done at the nadir. Also, at least one pooled meta-analysis suggests that after an initial decrease in the mean neutrophil counts, levels stabilize over the 6-month period. The BSR recommendation for MTX monitoring (2009) advises a monthly full blood count for the first 12 months and then, if appropriate, reduced to every 2–3 months thereafter. As TCZ is at least as likely to cause neutropenia as MTX, the above monitoring schedule for TCZ was felt by the working group to be justified.

Does TCZ therapy in RA affect liver function and how should this be monitored?

The use of TCZ is associated with abnormalities of liver function tests. Transient elevation in liver enzymes was noted relatively frequently, however, dose modification was required infrequently in clinical trials [13, 25–28].

Combination therapy of TCZ with conventional DMARDs has been shown to be associated with a transient elevation in alanine transaminase (ALT) levels in approximately half of patients, with levels being less than three times the upper limit of normal (ULN) in 41–51% of patients [14, 26, 27, 28]. In patients on TCZ monotherapy, elevation of ALT was seen at a similar rate of frequency compared with MTX monotherapy [13, 19]. In a study by Schiff *et al.* [19], pooled data from five pivotal RCTs were analysed and suggested that ALT elevation in patients on combination therapy was more frequent than with monotherapy with either TCZ or MTX (Table 2). The increase in ALT has been shown to follow a saw-tooth pattern, with levels rising and then falling in the interval between infusions [12]. Data from long-term extension studies appear to indicate that TCZ is safe and the rates of ALT elevation tend to be similar to those seen in RCTs [11, 24].

An elevation in bilirubin levels has also been noted in association with TCZ use. In the AMBITION study [13], which compared TCZ monotherapy with MTX monotherapy, 7.6% of patients had elevated serum bilirubin levels compared with 0.7% of patients on MTX. The rates with combination therapy are similar (9% with TCZ + conventional DMARDs, 0.9% with placebo + convention DMARDs in the TOWARD study [26]).

TABLE 2 Pooled analysis of data from the double-blind controlled phase of the AMBITION, OPTION, TOWARD, RADIATE and LITHE

	TCZ + conventional DMARDs, %	TCZ monotherapy, %	MTX monotherapy, %	Non-MTX DMARD therapy, %
ALT <3 × ULN	46	34	32	19
ALT >3 × ULN	6	2	4	1

Adapted from Schiff et al. [19]. ALT: alanine transaminase; ULN: upper limit of normal.

The increases in bilirubin did not appear to coincide with increases in ALT. The significance of this is uncertain, but reassuringly, progressive hepatic dysfunction has not been reported.

The TCZ SPC recommends the following with regards to abnormalities in liver function tests. When ALT is greater than one to three times ULN, it is recommended that the dose of MTX be modified if appropriate. For persistent elevations at this level, a TCZ dose reduction to 4 mg/kg is recommended until ALT levels normalize. When the ALT is greater than three to five times ULN, the SPC recommends that TCZ therapy be interrupted until levels fall below three times ULN. In patients with ALT greater than five times ULN, the SPC recommends that TCZ be discontinued.

Recommendations

(i) Liver function tests should be monitored in all patients receiving TCZ either as monotherapy or in combination with conventional DMARDs at 4-week intervals. In patients receiving TCZ monotherapy, if no liver test abnormalities are detected at the end of 6 months, less frequent monitoring (every 2–3 months) may be acceptable. In patients on combination therapy with conventional DMARDs including MTX, as the incidence of liver test abnormalities is considerably higher, we recommend that 4-week tests be continued for the duration of TCZ therapy. We recommend that tests be carried out in the week leading up to the next infusion (level of evidence 2+, grade of recommendation D, working group consensus score 9.4/10).

(ii) The effect of other hepatotoxic drugs and alcohol on liver enzymes has not been studied. We recommend that hepatotoxic drugs be used cautiously in patients on TCZ, particularly if they are also receiving MTX, and that clinicians follow the same alcohol consumption recommendations as they would for patients on MTX (level of evidence 4, grade of recommendation D, working group consensus score 9.4/10).

Special considerations

In patients with RA, is TCZ therapy associated with increased risk of post-operative infection and how should the dosing regimen be modified in patients undergoing elective surgery?

IL-6 expression is increased during surgery even in the absence of infection. Surgical procedures with greater tissue trauma are associated with higher plasma levels of IL-6 compared with less invasive procedures [29]. The significance of this is unclear, although it has been suggested that IL-6 may play a role in wound healing. To date, there is no evidence pointing to delayed wound healing or increased risk of post-operative infection in patients receiving TCZ. In a retrospective case cohort study by Hirao et al. [30], the non-interrupted use of TCZ prior to elective joint replacement surgery was associated with a statistically significant reduction in febrile response and lower CRP levels compared with patients on conventional DMARDs undergoing similar procedures. In another small case–control study, Hiroshima et al. [31] demonstrated a similar statistically significant reduced CRP and temperature response despite a 4-week interruption of TCZ therapy prior to joint replacement surgery. Neither of these studies was powered to look at post-operative infection risk. There was no statistically significant difference in white cell count between the TCZ patients and controls in either study.

Withdrawal of active treatment prior to surgery in patients with RA can result in a disease flare, which in turn can impact post-operative rehabilitation. Indeed, in a real-life retrospective review of all orthopaedic surgeries in patients with RA receiving TCZ, Momohara [32] identified 3 post-operative infections, 20 episodes of delayed wound healing and 36 cases of RA flare. In his evaluation of 166 surgeries over 11 years, a statistically significant association was found between delayed wound healing and the use of corticosteroids [$P = 0.046$, odds ratio (OR) = 5.7].

Recommendations

(i) In patients with RA undergoing elective joint replacement surgery, a 4-week interruption of TCZ is advised prior to surgery to reduce the risk of post-operative infection (level of evidence 2−, grade of recommendation D, working group consensus score 9.5/10). In these patients, clinicians are advised to be highly vigilant for clinical signs of infection and not to rely on CRP and body temperature when assessing for infection in the post-operative period. An increase in the neutrophil count or even a small increase in temperature or CRP in these patients should warrant further assessment. TCZ should be recommenced post-operatively, in consultation with the surgical team, once infection is excluded and the wound has healed. Overall the risk of infection and theoretical risk of delayed wound healing should be balanced

against the risks of perioperative RA flare (level of evidence 4, grade of recommendation D, working group consensus score 9.5/10).

(ii) In non-orthopaedic procedures similar recommendations should be followed, although data in this area are lacking (level of evidence 4, grade of recommendation D, working group consensus score 9.5/10). Particular caution should be exercised in patients undergoing bowel surgery due to the potential risk of bowel perforation.

In patients with RA, is TCZ safe for use during pregnancy and breastfeeding?

Management of RA during pregnancy and lactation poses a particular challenge to the rheumatologist, as all biologic agents and most conventional DMARDs are contraindicated during this period. Formal evaluation of their safety in this situation is not possible. Unfortunately, pregnant women are more likely to be treated with high-dose corticosteroids, with ensuing side effects. Conversely there is some evidence that high levels of circulating IL-6 may be deleterious to the fetus. In a Dutch study [33] of 161 pregnant women compared with 32 controls, high maternal IL-6 was associated with low neonatal birth weight ($P < 0.01$). In a review article published last year, Prins *et al.* [34] summarized the currently available evidence and inferred that high bioavailability of IL-6 is associated with changes in the reproductive tract that may increase the risk of recurrent miscarriage.

As TCZ contains an Fc fragment, active transfer across the placental barrier is possible, although data regarding this are currently lacking. In animal models, no teratogenic effects have been noted at any dose, but high dose (>100 times the human dose) was associated with an increased risk of spontaneous abortion and fetal death [1].

In TCZ trials, women of childbearing age were required to use contraception. Rubbert-Roth *et al.* [35] presented pooled pregnancy data from all TCZ clinical trials at the ACR conference in 2010. Thirty-three pregnancies occurred in 32 patients. Thirteen pregnancies were therapeutically aborted. Seven spontaneous abortions occurred and 11 pregnancies resulted in term deliverys, of which one neonate died of respiratory distress syndrome.

There are no data on the safety of TCZ during breastfeeding. Most TCZ trials did not require male patients to use contraception and there is no such requirement for this in the TCZ SPC.

Recommendations

(i) In women with RA currently being treated with TCZ, the drug should be stopped at least 3 months prior to planned conception (level of evidence 4, grade of recommendation D, working group consensus score 9.4/10).

(ii) In patients who choose to breastfeed, TCZ must only be reinstituted once the infant has been weaned off breast milk completely (level of evidence 4, grade of recommendation D, working group consensus score 9.4/10).

In patients with RA on TCZ is vaccination safe and effective?

Consistent with other biologic DMARDs, the use of live vaccination is contraindicated while on TCZ therapy. The efficacy of inactivated vaccines (particularly the influenza vaccine) is reduced in patients on anti-TNF therapy, however, sero-conversion rates remain high enough to justify vaccination. Only one study has looked at influenza vaccine sero-protection rates in TCZ-treated RA patients. In an open-label study [36], 194 patients with RA on TCZ were classified into four groups: TCZ monotherapy, TCZ + MTX, MTX monotherapy and placebo. All patients received a single dose of the trivalent influenza vaccine and sero-protection rates exceeded 70% in all groups. None of the patients experienced systemic adverse effects or flares of disease.

Recommendations

(i) Influenza vaccination is likely to be safe and effective in patients on TCZ. All patients on TCZ should be encouraged to have the annual influenza vaccine (level of evidence 3, grade of recommendation D, working group consensus score 9.9/10). The same guidance can be applied to pneumococcal vaccination (although data on efficacy are lacking).

(ii) Due to the associated immunosuppression, and as with any biologic or non-biologic DMARD, live attenuated vaccines are contraindicated in patients on TCZ (level of evidence 4, grade of recommendation D, working group consensus score 9.9/10).

In patients with RA, does treatment with TCZ increase the risk of GI perforation?

Cases of GI perforation have been reported with the use of TCZ in patients with RA. According to the TCZ SPC [1], the overall rate of GI perforation during the 6-month double-blind clinical trials was 0.26 events per 100 patient-years of exposure to TCZ and 0.28 events per 100 patient-years in the long-term extension studies. In a pooled meta-analysis of five RCTs and two long-term extension studies, Schiff *et al.* [19] reported GI perforation occurring at a rate of 2.0 per 1000 patient-years in the all-control population (patients assigned to the control group in all five RCTs) and 2.8 per 1000 patient-years in the all-exposed population (patients that received at least one dose of TCZ). The same data were presented in abstract form [37] and 16 of the 18 cases of lower GI perforation occurred in patients with diverticulitis, with the majority of patients having been treated concomitantly with corticosteroids and NSAIDs. In a systematic review by Gout *et al.* [38], the risk of diverticular perforation with TCZ was found to be slightly higher than with anti-TNF drugs and lower than with corticosteroids and NSAIDs.

Curtis *et al.* [39] evaluated the incidence of GI perforation in patients with RA by interrogating the administrative databases of a large US health plan. All cases of hospitalization due to GI perforation that occurred between 1 January 2005 and 31 August 2009 were evaluated. From their analysis, the rate of GI perforation in patients currently on biologic DMARDs and steroids was found to be 1.12 per 1000

patient-years (95% CI 0.5, 2.49), whereas in those not receiving corticosteroids it was 0.47 (95% CI 0.22, 0.98). According to the authors, current treatment with biologic DMARDs and/or MTX did not confer an increased risk of GI perforation (hazard ratio 1.5, 95% CI 0.7, 3.2). In contrast, the use of corticosteroids and NSAIDs posed a significant risk (hazard ratio 4.7, 95% CI 1.9, 12) and a previous history of diverticulitis conferred the highest risk for GI perforation (hazard ratio 9.1, 95% CI 3.1, 26.4).

Recommendation

(i) In RA patients with a previous history of diverticulitis, TCZ must be used with caution. In those who are concomitantly on corticosteroids and/or NSAIDs, the risk of GI perforation may be significantly higher. If used, we recommend such patients be counselled regarding the risk and that they be told to seek urgent medical attention if abdominal symptoms develop (level of evidence 3, grade of recommendation D, working group consensus score 9.9/10).

Concluding remarks

The working group recognizes that various barriers may exist in relation to implementation of this guideline, an important one being the lack of NICE approval for the use of TCZ in monotherapy. It is felt that the evidence presented here will help to facilitate the implementation of this guideline by providing clinicians with an evidence-based rationale in order to overcome such hurdles.

The guideline does not address the cost-effectiveness of TCZ, and this is an area that may need further evaluation, although this is the purview of NICE. However, the working group did not see any significant resource implications in the implementation of this guideline.

Another area not covered by this guideline is the use of s.c. TCZ. It is envisaged that the guideline will require updating when further data on the efficacy and tolerability of s.c. TCZ become available. Lastly, the BSR strongly recommends that any patient starting on a biologic for RA be registered on the BSR Biologics Register. Please check www.rheumatology.org.uk/BSRBR_now_recruiting to see if your patient is eligible.

Areas for further research

(i) In patients with RA and an inadequate response to TCZ, does a shorter dosing interval confer improved efficacy without an increase in side effects?
(ii) In RA, what are the criteria for withdrawal of therapy in patients with a poor response?
(iii) In RA, what are the criteria for withdrawal of therapy in patients in remission?
(iv) In patients with RA, what is the effect of TCZ on other drugs that are metabolized by the cytochrome P450 system?

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