ABSTRACTS IN PERSPECTIVE

Treatment Effects and Considerations for IL-6 Inhibition in Rheumatoid Arthritis

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Disease-modifying antirheumatic drugs (DMARDs), most notably methotrexate (MTX), have become the "anchor drugs" for the treatment of rheumatoid arthritis (RA), as studies clearly demonstrate that early treatment with these agents can prevent joint damage and long-term disability in RA patients. However, some patients do not adequately respond to DMARDs or lose their response over time and thus biologic agents such as tumour necrosis factor (TNF) inhibitors may be required to reduce disease activity and reduce the risk of radiologic progression. Most recently, the IL-6 receptor antagonist tocilizumab has been shown to bind specifically to both soluble and membrane-expressed IL-6 receptors, thereby reducing the pro-inflammatory effects of IL-6 and providing another option in targeting the inflammatory cascade in RA

The RAISE Survey

A survey carried out in nine countries, including Canada, by McInnes et al. has provided insight into how well RA patients respond to usual care. In the RAISE (Rheumatoid Arthritis: Insights, Strategies and Expectations) survey, a total of 586 RA patients were interviewed. There were approximately 30 biologic-naive patients and 35 on anti-TNF therapy per country. The biologic-naive patients were eligible for biologic therapy based on disease activity criteria.

Patients were asked to rate the proportion of "good" or "bad" days they had each month. Overall, patients rated two out of three days per month as "good," however, for patients treated with a biologic, the proportion of "good" days was significantly higher at 71% than biologic-eligible patients at 61%. Furthermore, significantly more biologic-eligible than biologic-experienced patients (25% vs. 19%) reported severe pain.

Among all respondents, 19% did not work because of their disease and of those who did work, 32% had lost one or more days of work in the past three months (mean 6.5 days lost) because of their RA. After receiving a biologic, patients reported being more efficient, taking less sick leave and increasing the number of working days following initiation of their therapy, and significantly more biologic-treated patients reported being satisfied with their current medication than those who were biologic-naive.

The RAISE survey demonstrates that there is a considerable unmet need in the treatment of RA and that biologic therapy is associated with better patient outcomes. The results support the premise that practitioners should aim to achieve and sustain clinical remission as early as possible in the course of the disease.

Feasibility of a DAS28-driven Strategy

While this goal has been met in a clinical trial setting, achieving it a real-world setting can be more challenging. Schipper et al. sought to determine if a tight Disease Activity Score (DAS)28-driven step-up strategy was more effective than usual care in helping real-world patients achieve remission over the course of a year-long study.

The step-up cohort first received MTX then additional sulfasalazine (SSZ). If by week 24 patients were not in DAS28 remission (<2.6), then SSZ was changed to anti-TNF therapy. The usual-care group mainly received MTX or SSZ monotherapy at the discretion of the treating rheumatologist.

At the end of one year, 55% of patients treated with the tight control strategy had achieved a DAS28 remission vs. 30% of the usual-care group. In updated data presented, the median time to first remission was also significantly longer for the usual-care group at over 52 weeks vs. 25 weeks for the tight control group, and DAS28 also dropped significantly more from baseline (-2.5) than in the usual-care group (-1.5).

Investigators concluded that a therapeutic regimen guided by DAS-28 remission criteria is feasible in clinical practice and that such a strategy putss more patients into remission in a shorter period of time than usual care.

Long-term Maintenance of Treatment Response

A comprehensive clinical trials program continues to support IL-6 inhibition as an appropriate strategy in patients who do not achieve an adequate response to either DMARDs or anti-TNFs. Based on an analysis of five randomized controlled trials (RCTs) plus three long-term extension studies presented by Smolen et al., the efficacy of TCZ has been shown to stabilize or even increase over time.

At 180 weeks, 17% of patients who had inadequate response to DMARD therapy (DMARD-IR) maintained an ACR70 response for 48 weeks. At 156 weeks, maintenance of an ACR70 response for 48 consecutive weeks was achieved by 18% of the group who had never been exposed to or who had never failed MTX, by 10.5% of those with an inadequate response to anti-TNF therapy (anti-TNF-IR), and by 16% of the DMARD-IR group.

Decreases in both mean tender joint counts (TJC) and swollen joint counts (SJC) were also well maintained in all groups. Proportions of patients who achieved 0 SJC and 0 TJC were 40.9% and 25.1%, respectively, in the never exposed or failed MTX group, 22.9% and 14.8% in the anti-TNF group and 35.7% and 26.7% in the DMAR-IR group. The number of DMARD-IR patients who achieved a low disease activity score ($\leq$3.2) or DAS28 remission ($\leq$2.6) increased over the initial year of treatment through to week 84 and week 72, respectively. Long-term safety data indicate there were no new safety signals from exposure to TCZ after 2.4 years of follow-up.

Further evidence of long-term efficacy is provided by the LITHE trial, a primarily radiographic study that compared the combination of TCZ plus MTX vs. MTX alone. At two years, patients in the TCZ 8 mg/kg group had significantly less radiographic progression (81% inhibition) vs. control patients. The total Sharp-Genant score for the MTX arm was significantly higher at 1.96 compared to 0.37 and 0.58 for the TCZ 8 and 4 mg/kg arms, respectively.

At two years as well, significantly more patients in the TCZ 8mg/kg (82%) had no radiographic progression compared to the MTX control arm (60%). Patients that were rescued to TCZ 8mg/kg showed additional benefit between the first and second year.

Clinical responses (ACR20/50/70 plus DAS28 remission) along with low disease activity rates improved continuously across the two-year study as well, as did improvement in physical function. Patients initially randomized to TCZ 8mg/kg showed DAS remission rates of 48% at week 52 and continued to increase to 65% at week 104. The safety profile in LITHE was also consistent with longer-term follow-up, serious AE rates being low and similar across the three treatment arms.

Activity in Patients with High Disease Activity

In a setting closely resembling real-life medical care, the open-label TAMARA (Tocilizumab and DMARDs: Achievements in Rheumatoid Arthritis) trial was carried out in RA patients with a high mean baseline DAS of 7.7. As investigators reported, at week 4, clinically relevant reduction in disease activity was observed with patients achieving a mean DAS of 4.9 and reducing to 3.9 at 24 weeks. From Day 1 to 28 steady improvements in patient-reported outcomes was noted, including significant improvements in pain, fatigue and morning stiffness. These improvements were maintained over 24 weeks.

Safety Update

As presented by van Vollenhoven et al., occurrence rates per 100 patient-years of serious adverse events (AEs) and serious infections were 14.4 and 4.7, respectively. Comparable rates among controls were 14.4 and 3.4, respectively. Gastrointestinal (GI) perforation rates were also low and in line with rates reported in other databases. All GI perforations in the long-term safety analysis occurred in patients who had at least one risk factor for such an event such as histoty of diverticulitis or concomitant NSAID and steroid use. Malignancy rates were low (1.1 per 100 patient-years), as were rates for myocardial infarction and stroke.

While studies suggest that RA patients have decreased lipid levels, increases in total cholesterol largely driven by increases in LDL-C have been reported with anti-TNF therapy. However, as reported by Curtis et al., lipid levels only go up about 5 mg/dL in patients on introduction of an anti-TNF agent. LDL-C levels did increase in some patients on initiation of TCZ treatment, but so did HDL-C levels and the net effect of lipid changes on cardiovascular disease (CVD) risk is difficult to assess. Given that RA patients appear to be at greater risk for CVD than the general population, it may be prudent to consider a statin in anti-TNF or IL-6 inhibitor candidates, especially if they are not at recommended LDL-C targets. Patients on TCZ initiating lipid-lowering therapy generally responded to treatment without complications.

Elevations in liver enzymes >3x ULN occurred infrequently and no evidence of clinical hepatitis or drug induced liver injury was associated with ALT/AST elevations in patients treated with TCZ.

Acute Phase Response

IL-6 inhibition significantly reduces acute phase response (APR) in the liver and a study assessed whether or not TCZ's effect on APR contributes to response and remission rates. The analysis by Smolen et al. demonstrated that only about 10% of responders fulfilled three out of five additional ACR criteria, suggesting that some 90% of responders achieve an ACR20 response independent of TCZ's effect on APR. These are similar to data obtained with the anti-TNF infliximab in the ATTRACT trial.

RA and Fatigue

In RA trials in which fatigue was measured, a comparison of traditional vs. biologic DMARDs suggests that the biologics appear to be associated with less fatigue, according to Campbell et al. Although the reasons for this remain uncertain, the OMERACT initiative recommends adding fatigue to measures of overall study outcomes. ■

COMMENTAIRE ÉDITORIAL :

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Les agents de rémission (communément appelés «DMARD»), en particulier le méthotrexate (MTX), sont aujourd'hui la pierre angulaire du traitement de la polyarthrite rhumatoïde (PR), et pour cause : les études démontrent clairement que le recours précoce à ces agents peut prévenir les lésions articulaires et l'invalidité à long terme. Malheureusement, chez certains patients, la réponse est insuffisante ou s'atténue avec le temps. Le cas échéant, on doit parfois se tourner vers les agents biologiques tels les inhibiteurs du facteur de nécrose tumorale (anti-TNF) pour atténuer l'activité de la maladie et réduire le risque de progression radiologique. Récemment, on a montré que le tocilizumab (TCZ), antagoniste des récepteurs de l'interleukine-6 (IL-6), se liait de manière spécifique aux récepteurs solubles et membranaires de l'IL-6, diminuant du coup les effets pro-inflammatoires de cette interleukine. Nous disposons dès lors d'une nouvelle cible pour agir sur la cascade inflammatoire de la PR.

Sondage RAISE

Un sondage réalisé dans neuf pays, dont le Canada, par McInnes et ses collègues a permis d'évaluer la réponse de la PR au traitement usuel. Au total, 586 patients atteints de PR ont répondu au sondage RAISE (*Rheumatoid Arthritis: Insights, Strategies and Expectations*). Dans chaque pays, environ 30 répondants n'avaient jamais reçu de biothérapie et 35 étaient sous anti-TNF. Les répondants jamais traités par un agent biologique étaient, vu l'activité de leur PR, des candidats à ce type de traitement.

On a demandé aux patients d'évaluer la proportion mensuelle de «bonnes» et de «mauvaises» journées. Deux journées sur trois ont été qualifiées de «bonnes» par l'ensemble des répondants; cependant, la proportion de «bonnes» journées était significativement plus élevée chez les patients sous biothérapie que chez les candidats à la biothérapie (71 % vs 61 %). Qui plus est, ces derniers ont été plus nombreux à se plaindre de douleurs intenses que les patients traités par un agent biologique, et l'écart était significatif (25 % vs 19 %).

Au total, la PR empêchait 19 % des répondants de travailler, et parmi ceux qui étaient sur le marché du travail, 32 % s'étaient absentés au moins une journée au cours des trois mois précédents (6,5 jours d'absence en moyenne) en raison de la PR. Par ailleurs, les patients sous biothérapie ont affirmé qu'après l'amorce de ce traitement, ils ont été plus efficaces, se sont absentés moins souvent et, partant, ont consacré plus de journées au travail. Enfin, la proportion de répondants satisfaits de leur médicament était significativement plus élevée chez les patients sous biothérapie que chez les candidats à la biothérapie.

Le sondage RAISE démontre que les besoins thérapeutiques sont loin d'être comblés dans la PR et que les agents biologiques donnent de meilleurs résultats cliniques. De plus, il vient étayer la prémisse selon laquelle les cliniciens devraient s'employer à amener et à maintenir le patient en rémission clinique le plus tôt possible dans le cours de la maladie.

Traitement en fonction du score DAS28 : une stratégie envisageable?

Bien que le traitement balisé en fonction du score DAS28 (*Disease Activity Score*) ait fonctionné lors d'essais cliniques, son application réelle dans la population peut se révéler plus laborieuse. Schipper et ses collaborateurs ont tenté de déterminer, au cours d'une étude de un an menée dans un contexte réel, si une stratégie de puissance progressive rigoureusement régie par le score DAS28 était plus efficace que la prise en charge usuelle pour l'obtention d'une rémission.

La cohorte sous traitement de puissance progressive a d'abord reçu du MTX, auquel on a ajouté de la sulfasalazine (SSZ). À 24 semaines, on a substitué un anti-TNF à la SSZ chez les patients qui n'étaient toujours pas en rémission DAS28 (<2,6). Dans la cohorte sous traitement usuel, la plupart des sujets ont reçu du MTX ou de la SSZ en monothérapie, au gré du rhumatologue traitant.

Après un an, 55 % des patients soumis au traitement rigoureusement balisé étaient en rémission selon le score DAS28 contre 30 % des patients soumis au traitement usuel. En outre, selon les données actualisées, l'intervalle médian entre le début de l'étude et la première rémission a été significativement plus long dans le groupe sous traitement usuel, soit au-delà de 52 semaines, que dans le groupe sous traitement rigoureusement balisé, soit 25 semaines; au surplus, le score DAS28 a diminué davantage par rapport à la valeur de départ dans ce dernier groupe que dans le groupe traité de la manière habituelle, et l'écart était significatif (-2,5 vs -1,5).

Conclusion des chercheurs : un traitement axé sur l'obtention d'une rémission selon le score DAS28 est réalisable en clinique et conduit plus rapidement à la rémission chez un plus grand nombre de patients que la prise en charge usuelle.

Maintien à long terme de la réponse

Selon un vaste programme d'essais cliniques, l'inhibition de l'IL-6 en cas de réponse inadéquate aux agents de rémission ou aux anti-TNF demeure pertinente. Selon une analyse de cinq essais comparatifs avec randomisation et de trois prolongations d'études à long terme réalisée par Smolen et ses collègues, l'efficacité du TCZ se stabilise, voire augmente au fil du temps.

À 180 semaines, la réponse ACR70 se maintenait depuis 48 semaines chez 17 % des patients dont la réponse aux agents de rémission s'était révélée inadéquate (AR-RI). À 156 semaines, le maintien de la réponse ACR70 pendant 48 semaines consécutives avait été constaté chez 18 % des patients jamais exposés au MTX ou chez lesquels cet agent n'avait jamais échoué, 10,5 % des patients dont la réponse aux anti-TNF s'était révélée inadéquate (anti-TNF-RI) et 16 % du groupe AR-RI.

Par ailleurs, la baisse de la valeur moyenne du nombre d'articulations douloureuses (NAD), d'une part, et du nombre d'articulations gonflées (NAG), d'autre part, s'est également maintenue dans tous les groupes. Les valeurs 0 NAD et 0 NAG ont été atteintes chez 40,9 % et 25,1 % des sujets du groupe jamais exposé au MTX ni à l'échec de cet agent, 22,9 % et 14,8 % du groupe anti-TNF-RI ainsi que 35,7 % et 26,7 % du groupe AR-RI. Le nombre de sujets AR-RI ayant obtenu un faible score d'activité morbide (≤3,2) ou une rémission DAS28 (≤2,6) s'est accru pendant la première année de traitement, puis jusqu'à la 84e semaine dans le premier cas et jusqu'à la 72^{e} semaine dans le deuxième. Sur le plan de l'innocuité à long terme du TCZ, il n'y avait rien de nouveau à signaler après 2,4 années de suivi.

L'efficacité à long terme du TCZ a également été montrée dans l'essai LITHE, lors duquel on a comparé l'association TCZ+MTX au MTX seul en fonction de paramètres essentiellement radiographiques. À 2 ans, la progression radiographique était significativement moindre (inhibition de 81 %) chez les patients du groupe TCZ à 8 mg/kg par rapport aux témoins. Le score Sharp-Genant total était significativement plus élevé dans le groupe MTX que dans les groupes TCZ à 8 et 4 mg/kg (1,96 comparativement à 0,37 et à 0,58, respectivement).

Toujours à 2 ans, le nombre de sujets exempts de progression radiographique était significativement plus élevé dans le groupe TCZ à 8 mg/kg (82 %) que dans le groupe MTX (60 %). Un bénéfice additionnel a été observé, entre la première et la deuxième année, chez les sujets ayant reçu du TCZ à 8 mg/kg en traitement de secours.

On a également noté une amélioration constante, au cours des deux années de l'étude, de la proportion de patients affichant une réponse clinique (ACR20, 50 et 70, et rémission DAS28), un faible score d'activité de la maladie et une meilleure capacité physique. En effet, chez les patients affectés dès le départ au groupe TCZ à 8 mg/kg, le taux de rémissions DAS s'est chiffré à 48 % à 52 semaines et a continué de s'élever pour atteindre 65 % à 104 semaines. Enfin, le profil d'innocuité dans la population LITHE rappelle celui qui ressort d'une plus longue observation, le taux d'effets indésirables graves ayant été faible et comparable dans les trois groupes.

Activité morbide en présence d'un score DAS élevé

L'essai ouvert TAMARA (*Tocilizumab and DMARDs: Achievements in Rheumatoid Arthritis*), mené dans un contexte proche de la réalité, réunissait des patients atteints de PR et présentant au départ un score DAS moyen élevé, soit 7,7. Ce score moyen a subi un recul cliniquement significatif, puisqu'il se situait à 4,9 après 4 semaines et à 3,9 après 24 semaines. Du premier au 28e jour, on a noté une amélioration constante des paramètres évalués par les patients eux-mêmes, l'amélioration ayant été significative au chapitre de la douleur, de la fatigue et de la raideur matinale. Précisons que ces améliorations se sont maintenues sur une période de 24 semaines.

Données récentes sur l'innocuité

Le taux de survenue d'effets indésirables graves et d'infections graves s'est situé, respectivement, à 14,4 et 4,7 pour 100 années-patients, rapportent van Vollenhoven et son équipe. Chez les témoins, ces mêmes taux ont atteint 14,4 et 3,4. Le taux de perforations digestives a également été faible et proche des taux signalés dans d'autres bases de données. L'analyse à long terme de l'innocuité a révélé que ces perforations s'étaient toutes produites chez des patients qui présentaient au moins un facteur de risque pertinent, par exemple des antécédents de diverticulite ou la prise concomitante d'un AINS ou d'un corticostéroïde. Enfin, on n'a enregistré qu'un faible taux de cancers (1,1 pour 100 années-patients), d'infarctus du myocarde et d'accidents vasculaires cérébraux.

Bien que des études donnent à penser que les taux lipidiques sont abaissés dans la PR, on a fait état d'une hausse du cholestérol total, largement imputable à l'augmentation du C-LDL, chez des patients sous anti-TNF. Cependant, signalent Curtis et ses collaborateurs, les valeurs lipidiques ne s'élèvent que de 5 mg/dL environ lors de l'amorce d'un traitement anti-TNF. Le C-LDL a effectivement augmenté au début du traitement par le TCZ, mais le C-HDL en ayant fait tout autant, il est difficile d'évaluer l'effet net des variations lipidiques sur le risque cardiovasculaire. Cela dit, comme les patients atteints de PR semblent plus exposés aux maladies cardiovasculaires que la population générale, peut-être serait-il prudent de prescrire une statine au début du traitement par un anti-TNF ou un inhibiteur de l'IL-6, a fortiori en présence d'un taux de C-LDL supérieur à la valeur cible. La plupart des patients sous TCZ qui ont amorcé un traitement hypolipidémiant y ont bien répondu, sans subir de complications.

Enfin, les taux des enzymes hépatiques se sont parfois élevés à plus de trois fois la limite supérieure de la normale, mais ces hausses ont été peu fréquentes. Aucun signe d'hépatite clinique ni de lésion hépatique iatrogène n'a été associé à l'augmentation des taux d'ALT et d'AST chez les patients traités par le TCZ.

Réponse de phase aiguë

L'inhibition de l'IL-6 atténue significativement la réponse de phase aiguë (RPA) dans le foie. Des chercheurs se sont demandé si l'effet du TCZ sur la RPA contribuait aux taux de réponse et de rémission. Smolen et son équipe ont démontré qu'environ 10 % seulement des répondeurs satisfaisaient à trois autres critères de RPA sur cinq, ce qui porte à croire qu'environ 90 % des répondeurs obtiennent une réponse ACR20 indépendamment de l'effet du TCZ sur la RPA. On avait obtenu des résultats similaires avec l'infliximab, un anti-TNF, lors de l'essai ATTRACT.

PR et fatigue

Dans les essais sur la PR lors desquels on a évalué la fatigue, Campbell et ses collègues ont constaté que les agents de rémission biologiques semblaient causer moins de fatigue que les agents de rémission classiques. Bien que l'on s'explique encore mal cette différence, le réseau OMERACT recommande l'ajout de la fatigue aux paramètres d'évaluation des études. ■

Rheumatoid Arthritis: Insights, Strategies and Expectations—Global Results of the RAISE Patient Needs Survey

I. B. McInnes, B. Combe, G. R. Burmester

Purpose: Understanding the perceptions of patients who live with rheumatoid arthritis (RA) and their views on its treatment can provide a valuable perspective to the rheumatologist and may help to shape our management strategies. The RAISE survey was designed to reveal the perceptions of RA patients on their disease and therapy.

Method: A questionnaire was developed with input from 53 rheumatologists from 8 European countries and Canada. Questions included, but were not limited to, the following topics: diagnosis, disease information sources, daily living with RA, quality of life (QoL) and views on current therapy and treatment options. Surveyed patients were either on biologic therapy or biologic naïve but eligible for biologic treatment based on broad criteria of a DAS28 >3.2 or an acute phase response, plus erosive disease and moderate-to-severe active RA.

Results: A total of 586 patients, approximately 30 biologic naïve and 35 on anti-TNF therapy from each of 9 countries, were interviewed. Mean age at onset of RA symptoms was 41 years. Patients reported that most physician-patient communication centered on symptoms and treatment; less frequently discussed was the impact of RA on QoL. While all patients reported improvement on their current versus previous treatment, biologic users had significantly more 'good' days per month than biologic-naïve patients (71% vs 61%, respectively). The survey revealed a large percentage of patients (22%) reporting high levels of pain. For most patients, biologic therapy improved their symptoms and overall QoL compared with their previous non-biologic therapy. Biologic-experienced patients were significantly more satisfied with their treatment than biologic-naïve patients. Patients (41%) use the internet as a resource for information about RA. Approximately 20% of biologic users require help (emotional and/or physical) in preparing and/or administering subcutaneous injections and have concerns around injection site pain or irritation. Despite being eligible for biologic therapy by a broad definition of criteria, 62% of biologic-naïve patients were not aware of biologic therapies and the majority (88%) were never recommended a biologic treatment. Factors influencing willingness to try a new medication included symptom control, stopping disease progression and improving the overall experience of living with RA. Patients were most interested in a product that worked consistently (76%), was simple to use (69%) and had a less frequent dosing schedule (75%).

Conclusion: This large patient survey provides key insights into how RA patients live with their disease and how therapy has impacted them. The data reveal that biologic therapy has had significant impact on improving patients' lives. However, all patients reported some level of continuing symptoms and current pain indicating unmet clinical need.

Commentary on abstract 1595

In order to improve RA management, physicians need to assess how well patients who are already being treated are coping. RAISE was a survey of patients with RA, a small proportion of whom were currently on anti-TNF agents, and a similar number who were eligible for biologic therapy but who were biologic-naive. On current treatment, patients rated two out of three days per month as being "good," with more biologic-treated patients having good days than biologic-naive patients. Despite therapy, 22% of patients described high levels of pain, with more biologic-naive (25%) than biologic-treated patients (19%) reporting severe pain. Almost one-fifth of respondents (19%) did not work because of their disease, while nearly one-third had lost at least one or more days of work in the last three months (mean 6.5 days). Compared to their pre-biologic days, biologic-treated patients reported greater productivity including reduced sick leave and increased number of working days. The high pain levels and the impact of the disease on productivity revealed by this survey, especially among biologic-naive patients, suggest there is an unmet need for better treatment of RA, as biologic-naive patients in particular had low satisfaction with their current treatment regimen.

Questions and answers with Dr. Iain McInnes, Centre for Rheumatic Diseases, University of Glasgow, UK

Q: How did patients rate their anti-TNF medication?

A: Patients indicated that treatment offered relief of their most severe symptoms including the most common ones such as hand and foot pain, where over half of patients who reported these symptoms reported relief. Overall, approximately 90% of patients on anti-TNF therapy indicated that treatment improved their symptoms and QoL compared with previous non-biologic treatment.

Q: Why did patients eligible for biologic therapy not receive it?

A: We found that only 38% of patients who were eligible for biologic therapy were actually aware of biologic treatment options for RA, and that the majority of biologic-naive patients (88%) had never been offered a biologic agent. This was in spite of the fact that patients indicated they were willing to try an injectable medication if the treatment was considered to be an important advance. So opportunities exist for improving communication between doctor and patient regarding the impact of the disease on patients' lives, as the majority of biologic-eligible patients want better treatment options.

Tight Control Aiming at a DAS28 Remission Is More Effective in Reaching High Remission Rates than Usual Care in Rheumatoid Arthritis.

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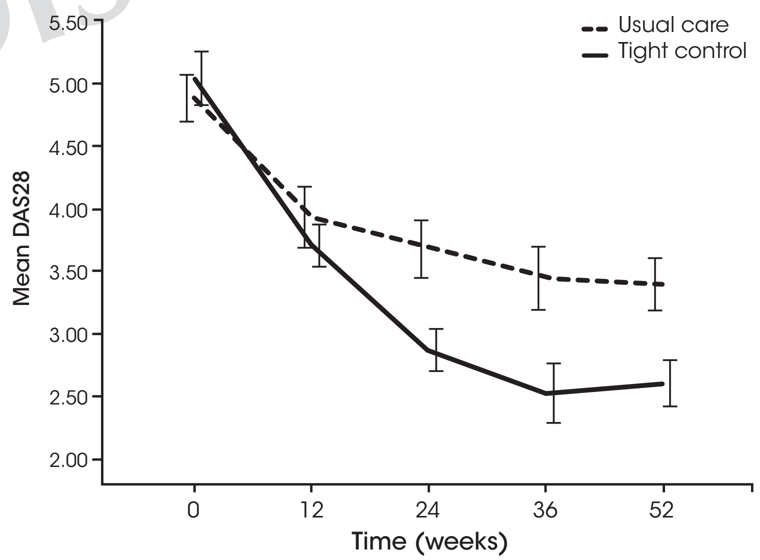
Purpose: The ultimate treatment goal in Rheumatoid Arthritis (RA) is to achieve and sustain clinical remission as early as possible. In clinical trials, tight control was shown to be very effective in achieving this goal. However, the question is in how far these promising results can be transferred into daily clinical practice. Therefore, the aim of this study was to investigate whether a tight control treatment strategy is more effective than treatment according to usual care in reaching remission after 1 year of follow-up in patients with early RA.

Methods: Two early RA inception cohorts from two different regions including patients who fulfilled the ACR criteria for RA and disease duration <1 year were studied. In both cohorts, DAS28 was evaluated every 3 months. Patients in the tight control cohort (n=126) were treated between 2006-2008 according to a DAS28-driven step-up treatment strategy starting with MTX, addition of SSZ, exchange of SSZ by anti-TNF. Patients in the usual care cohort (n=126) were treated between 2004-2008 and were mainly treated with MTX or SSZ monotherapy at discretion of the rheumatologist, thus without DAS28 guided treatment decisions. Primary outcome was the percentage of patients in remission (DAS28<2.6) after 1 year. Secondary outcome measure was the mean change in the DAS28 from baseline to 1 year.

Results: At baseline, the tight control and usual care cohorts were comparable: age 56 vs 59 years, 63% vs 74% rheumatoid factor positive, baseline DAS28 was 5.0 vs 4.8 and baseline HAQ 1.2 vs 0.9, except for female gender (62% vs 48%). After 12 months, 55% of patients in the tight control cohort had a DAS28<2.6, versus 30% of usual care patients (*P*<0.0001, OR 3.1 (95% CI 1.8-5.2), adjusted for baseline DAS28). The median time to first remission was 19 weeks for tight control and 26 weeks for usual care (*P*<0.0001). The DAS28 was decreased with -2.5 in the tight control cohort and -1.5 in the usual care cohort, the between-group difference adjusted for baseline DAS28 was 0.85 (95% CI 0.58-1.12, *P*<0.0001) (Figure 1).

Figure 1. Mean decrease of DAS28 in tight control and usual care groups.



Conclusion: In daily clinical practice, a tight controlled treatment strategy aiming for remission leads to more rapid and higher percentages of DAS28 remission after 1 year than treatment according to usual care.

Commentary on abstract 1618

A primary goal in RA is to achieve clinical remission as early as possible and maintain it. Clinical trials have shown tight disease control can achieve this goal but whether the same strategy can be transferred to clinical practice is another question. Using a DAS28-driven step-up strategy, investigators treated one cohort with MTX, then additional SSZ. Patients were then switched to a biologic if they had not achieved a DAS28 remission by week 24. The usual-care group mainly received MTX or SSZ monotherapy and were not guided by DAS28 decisions. At the end of one year, almost twice as many patients (55%) treated with the DAS28-driven strategy had achieved remission compared to 30% of the usual-care group. Updated results presented showed that the median time to first remission was also significantly shorter for the tight control group at 25 weeks vs. over 52 weeks for the usual-care group. The DAS28 score was also significantly lower in the tight control group, the difference between the two groups being 0.85 at one year. Investigators concluded that a therapeutic regimen guided by DAS28 remission criteria is feasible in clinical practice and that such a strategy puts more patients into remission in a shorter period of time than usual care.

Questions and answers with Marlowes Vermeer, MSc, Radboud University, Nijmegen Medical Center, The Netherlands

Q: What was the approach to the DAS28-driven step-up treatment strategy?

A: In the tight control group, we used MTX 15 mg/week, and at eight weeks, if patients were not in DAS28 remission, the dose could be increased to 25 mg/week. At 12 weeks, SSZ could be added and then at week 24, the first biologic could be given which is much sooner than a biologic would be given in any usual-care group. We also followed the tight control group much more closely than the usual-care group.

Q: If the goal of RA is to get patients into remission as early as possible, why is this approach not used in clinical practice?

A: I think the need to measure DAS28 at regular intervals may be too time-consuming in practice, and the logistics of applying tight control in daily practice are also difficult because patients have to be seen more often than usual-care patients and that may not be possible in many rheumatology practices. But we did this study in daily clinical practice—we didn't have a select group of patients for it, this was a real RA population in The Netherlands—so it suggests that such a strategy is feasible to do in a real-world setting.

Long-term Efficacy of Tocilizumab in Rheumatoid Arthritis for up to 3.5 Years

J.S. Smolen, J.J. Gomez-Reino, C. Davies, E. Alecock, A. Rubbert-Roth, P. Emery

Purpose: Efficacy and safety of tocilizumab (TCZ) in rheumatoid arthritis (RA) pts have been shown for up to 1 y in phase 3 trials and for up to 2.5 y in long-term extension studies. Efficacy data for up to 3.5 y are reported here.

Method: The analysis includes all pts who received ≥1 dose of TCZ in the randomized controlled studies OPTION, AMBITION, RADIATE, and TOWARD or in the long-term, open-label extension studies GROWTH95 and GROWTH96 (pts from the 4 randomized studies transitioned into GROWTH95 and GROWTH96). Also included are all pts who received ≥1 dose of TCZ in the 2-y controlled (with a 3-y follow-up) phase 3 study, LITHE. Pts were analyzed in 3 groups: inadequate responders to DMARDs (DMARD-IR), anti-TNF-IR pts, and monotherapy pts who never failed MTX (AMBITION). Outcomes, including ACR50/70, DAS28 remission rate (DAS28 ≤2.6), and low disease activity score (LDAS; DAS28 ≤3.2), were assessed every 12 wks from initial TCZ exposure to the cutoff date (Feb 6, 2009). Data are shown for a maximum of 180 wks, after which pt numbers were too low to draw conclusions. High clinical hurdles were examined, such as proportions of pts with HAQ-DI=0, ≤1 SJC, and ≤1 TJC at 96 wks. Pts who withdrew from treatment were categorized as missing for all time points thereafter. Pts with insufficient data at a given time point were excluded from analysis for that time point only.

Results: A total of 3986 pts were included. By the cutoff date, approximately 4% had discontinued due to insufficient therapeutic response and approximately 14% due to safety (including intercurrent illness). Efficacy of TCZ in DMARD-IR pts was demonstrated by increased numbers of pts who achieved ACR50 and ACR70 up to wks 72 and 96, respectively, and who achieved maintenance of ACR70 for 24 consecutive wks, LDAS, and DAS28 remission up to wk 72. Thereafter, proportions increased further or were maintained with continued TCZ up to wk 180 (Table). In anti-TNF-IR and monotherapy pts, the proportions achieving these end points increased or were maintained with continued TCZ treatment (not shown). At 96 wks, proportions in the DMARD-IR, anti-TNF-IR, and monotherapy groups with HAQ=0 were 15%, 8%, and 23%, respectively; the proportions with ≤1 SJC were 46%, 34%, and 55%, respectively; and the proportions with ≤1 TJC were 37%, 23%, and 35%, respectively.

Conclusion: Longer-term treatment with TCZ for up to 132 wk yielded RA efficacy outcomes at maintained proportions of pts (albeit with decreasing pt numbers). These results support TCZ as an effective long-term treatment for RA pts.

Week	0	24	48	72	96	120	144	168	180
No. pts with valid assessment	2904	2693	2429	2284	2173	1822	1257	602	363
ACR50, % (n)	—	35 (929)	45 (1085)	51 (1156)	53 (1157)	58 (1050)	59 (738)	64 (387)	67 (242)
ACR70, % (n)	—	16 (423)	24 (580)	30 (687)	31 (683)	36 (650)	38 (478)	46 (275)	45 (168)
No. pts with valid assessment	—	—	2350	2358	2220	1977	1436	779	480
ACR70 maintained for 24 consecutive wks, % (n)	—	—	8 (192)	14 (326)	16 (360)	19 (383)	21 (306)	22 (169)	22 (103)
No. pts with valid assessment	2889	2658	2385	2231	2104	1754	1211	571	344
LDAS, % (n)	2 (50)	43 (1137)	54 (1293)	62 (1380)	65 (1365)	69 (1212)	70 (848)	73 (414)	74 (256)
DAS28 remission, % (n)	1 (22)	27 (722)	40 (954)	47 (1050)	50 (1046)	54 (940)	56 (681)	58 (330)	62 (214)

Note: Data from DMARD-IR pts shown.

Commentary on abstract 413

Inhibition of pro-inflammatory activity via the IL-6 receptor represents a new approach to the treatment of RA. As the first agent in its class, TCZ has been evaluated in five randomized controlled trials (RCTs) plus three long-term extension studies, for a total of 3.5 years of follow-up. At maximum follow-up of 180 weeks in the DMARD-IR group and 156 weeks for the other two groups, the proportion of patients who achieved an ACR20, ACR50 or ACR70 response generally stabilized or increased over time. At week 180, 17% of DMARD-IR patients had maintained an ACR70 response for 48 weeks. By week 156, maintenance of an ACR70 response for 48 consecutive weeks was achieved by 18% of the never-exposed or never-failed MTX group and by 10.5% of the anti-TNF-IR group. Decreases in both mean TJC and SJC were also well maintained in all groups. Further, the number of DMARD-IR patients who achieved a low disease activity score or DAS28 remission both increased over the initial year of treatment through to week 84 and week 72, respectively. Similar patterns occurred in the other two groups as well.

Questions and answers with Prof. Josef Smolen, Medical University of Vienna, Austria

Q: What were the SJC and the TJC results in the three different patient groups?

A: Over 40% of patients in the never-exposed or never-failed MTX group had 0 SJC and over 25% of them had 0 TJC at week 96. These numbers were slightly lower for the DMARD-IR patients, where approximately 36% of them had 0 SJC and approximately 27% had 0 TJC. For the anti-TNF-IR patients, approximately 23% and approximately 15% had 0 SJC and 0 TJC, respectively.

Q: What do you think the long-term data are telling rheumatologists?

A: It's telling rheumatologists that TCZ continues to be effective over the short clinical trial interval that usually lasts only for a few months. Not only that, but the data also show that the most profound responses to TCZ such as low disease activity or remission appear to increase over time because the number of patients who achieved these states increased over time. So what we showed is that actual numbers of patients continue to respond to TCZ over time and it means that the compound acts long-term.

LITHE: Tocilizumab Inhibits Radiographic Progression and Improves Physical Function in Rheumatoid Arthritis Patients at 2 Years with Increasing Clinical Efficacy Over Time

R. Fleischmann, R. Burgos-Vargas, P. Ambs, E. Alecock, J. Kremer

Purpose: To report results of a 2-yr planned analysis of a double-blind, randomized controlled, phase 3 trial of TCZ in pts with moderate to severe RA who remained on MTX despite inadequate response.

Method: Pts were randomized (1:1:1) to receive TCZ + MTX (4 mg/kg [TCZ4] or 8 mg/kg [TCZ8]) or placebo + MTX (control [CON]) every 4 wks. Stepwise rescue therapy starting at wk 16 was allowed if pts did not respond (<20% improvement in SJC and TJC). At wk 52, all pts were required to initiate open-label TCZ8 for yr 2, unless they had achieved ≥70% improvement in SJC and TJC, allowing them to continue the blinded therapy they were receiving at the end of yr 1 to wk 104. Primary 2-yr end points were change from baseline in Genant-modified Total Sharp Score (GmTSS) and physical function (AUC of change from baseline in HAQ-DI). Linear extrapolation (GmTSS) or standardization (change in HAQ-DI) was used for missing data (post-rescue data set to missing). To examine impact of 2 yrs of treatment, efficacy end points were assessed over time for pts randomized to TCZ8, with LOCF for SJC and TJC for pts who received rescue therapy or withdrew from that time point.

Results: The ITT population consisted of 398 TCZ8, 399 TCZ4, and 393 CON pts. At 2 yrs, exposure rate per pt-yrs (PY) were 1320, 521.9, and 284.8 in TCZ8, TCZ4, and CON pts. More CON pts required rescue vs TCZ pts, and more TCZ pts remained on initial randomized therapy (Table A). At yr 2, pts in the TCZ8 group had significantly less radiographic progression (81% inhibition) vs CON pts (based on linear extrapolation of mean change in GmTSS on initial treatment for post-rescue data). Significantly more TCZ8 pts had no radiographic progression vs CON pts ($P \leq 0.0001$). AUC of change from baseline in HAQ-DI showed significant improvement in physical function in TCZ4 and TCZ8 vs CON pts (Table A). In pts initially randomized to TCZ8, low disease activity score (LDAS; DAS28 ≤3.2) was seen in >60%, and DAS28 remission (DAS28 <2.6) rates were ~50% at wk 52 and continued to increase to wk 104 (Table B). By wk 52, in pts treated with TCZ8, clinically significant improvements in SJC occurred (–10) that were maintained through wk 104. Rates/100PY for adverse events (AEs) were higher in TCZ8 and TCZ4 (263.6, 275.4) vs CON pts (251.4) while rates for serious AEs were comparable (11.4, 12.1, 10.9). Rates per 100PY of AEs leading to withdrawal and treatment modification were higher in TCZ8 and TCZ4 (7.4 and 32.5; 8.4 and 30.7) vs CON pts (4.8 and 20.4) and rates for death were comparable (0.6, 0.2, 0.4).

Conclusion: TCZ + MTX continues to inhibit radiographic progression and improve physical function with a clinical effect, as evidenced by improving DAS28 remission, LDAS, and SJC at 2 yrs and with a manageable safety profile.

Table A. Disposition and selected endpoints at 2 yr in ITT pts

	Initial Randomized Therapy		
	Placebo + MTX	**TCZ 4 mg/kg+MTX**	**TCZ 8 mg/kg+MTX**
Randomized, n	393	399	398
Disposition			
Withdrawals, % (n)	27 (104)	22 (89)	22 (88)
Completed, % (n)	73 (289)	78 (310)	78 (310)
Rescue, % (n)	50 (197)	24 (96)	15 (60)
Open-label TCZ8 at Week 52, % (n)	68 (267)	63 (252)	62 (248)
Remained on randomized therapy at Week 52, % (n)	9 (34)	20 (78)	21 (85)
Mean GmTSS change from baseline	1.96	0.58[a]	0.37[a]
No GmTSS progression, % (n/n)	66 (195/294)	75 (256/343)[b]	83 (292/353)[a]

[a]$P \leq 0.0025$ vs placebo +MTX; [b]$P = 0.0239$; (n/n)=pts with response/evaluable pts

Commentary on abstract 637

At one year, the LITHE study showed that treatment with TCZ significantly reduced the risk of radiographic progression, with almost 87% of patients in the high-dose combination arm experiencing no progression of joint erosion at one year vs. 70% of MTX controls. At week 104, the percentage of patients with no change from baseline in the total Sharp-Genant score (TSS) was 81% for patients in the TCZ 8 mg/kg (0.37) and 71% for TCZ 4 mg/kg arm (0.58). The TSS score for the MTX arm was significantly higher compared with both TCZ arms at 1.96. Between baseline and week 104, 82%, 73% and 60% of patients in the 8 mg/kg arm, the 4 mg/kg arm and the MTX am had no progression of joint damage, and additional patients in the 8 mg/kg arm experienced this benefit between the first and second year of therapy. Clinical responses as measured by ACR and DAS criteria, as well as improvement in physical function as measured by the HAQ-Disability Index (HAQ-DI) score, improved continuously over the two-year follow-up. Serious AEs rates were low and similar across treatment arms and very few patients discontinued treatment due to AEs.

Questions and answers with Prof. Josef Smolen, Medical University of Vienna, Austria

Q: What do you think these two-year data are telling rheumatologists about TCZ?

A: The LITHE study clearly shows that TCZ not only affects clinical aspects of the disease but also radiographic effects, which is the goal for every disease-modifying compound. This is very important as radiographic progression over time leads to irreversible loss of function. So these data confirm that TCZ is very effective at inhibiting damage to joints.

Q: Why is achievement of remission important from a patient's perspective?

A: Successful remission may help restore a patient's sense of freedom, without painful flare-ups or fear of long-term disability, so it's very important from a patient's perspective.

Table B. Clinical efficacy data in pts initially randomized to TCZ8

	Baseline TCZ8 mg/kg+MTX	Week 52 TCZ 8 mg/kg+MTX	Week 104 TCZ 8 mg/kg+MTX
LDAS, % (n/n)		64 (176/275)	76 (184/241)
DAS remission, % (n/n)		48 (132/275)	65 (156/241)
Mean SJC*	17 (n=398)	7 (n=397)	6 (n=397)
Mean TJC*	29 (n=398)	14 (n=397)	12

(n/n)=pts with response/evaluable pts. Post-rescue data set to missing. LOCF for missing SJC and TJC

Interim Results of the TAMARA Study—Effectiveness and Safety of the Interleukin-6 (IL-6) Receptor Antagonist Tocilizumab After 4 and 24 Weeks in Patients with Active Rheumatoid Arthritis (RA)

A. Rubbert-Roth, J. Braun, E. Feist, H.L. Kellner, G.R. Burmester

Purpose: The IL-6 receptor antagonist tocilizumab was shown to be a safe and effective treatment option for RA-patients with intolerance or inadequate response to conventional DMARDs (1, 2, 3, 4) as well as TNF-blockers in clinical trials (5). This study was performed to assess the effectiveness and safety of tocilizumab in a setting close to real-life medical care.

Method: TAMARA is a German multi-center, open-label, non-controlled Phase IIIb study over 24 weeks with one treatment arm of tocilizumab 8 mg/kg iv q4w. A total of 293 adult RA patients with inadequate response to conventional and/or biological DMARDs were enrolled at 70 sites. Primary endpoint is the proportion of patients achieving a DAS28 "low disease" (defined as ≤3.2) at Week24. Secondary endpoints include further DAS assessments, ACR responses, changes in CDAI, acute phase reactants, HAQ-DI, SF-36, FACIT fatigue scale, prognostic values of several baseline variables in terms of treatment outcome, and adverse events experience including adverse events of special interest according to the risk management plan.

Results: In this week 4 interim analysis, data of 218 patients (75% of women, mean age 55 years, 39% previously on TNF-blockers) were evaluated. As a relevant result, tocilizumab reduced disease activity and improved quality of life and fatigue in patients with RA after 4 weeks (Table 1). The mean CRP level was completely normalized already after 1 week. In 40 patients 49 SAEs were reported as of 1st June 2009. The most often reported SAEs were respiratory tract infections (n=11) followed by increased liver enzymes (n=6). No fatal event was reported so far.

Conclusion: Treatment with tocilizumab achieves rapid improvement of signs and symptoms of RA in a setting mimic real-life medical care. The favorable safety profile of Tocilizumab could be confirmed in this ongoing study. No unexpected or new safety issues were observed.

Table: Results of the Week 4 analyses

Variable	Baseline	Week 4	Change
DAS28	7.5±1.1	4.9±1.5	-2.6±1.3 (N=122)
CRP (mg/L)	23.4±42.8	4.8±13.4	-18.5±41.2 (N=169)
HAQ-DI	1.48±0,64	1.14±0,67	-0.33±0.47 (N=217)
FACIT-F (fatigue)	29.2±11.4	35.4±3.0	6.2±9.4 (N=216)

Note: Values are given as mean and standard deviation; N depicts the number of underlying observations for the calculation of changes

Commentary on abstract 412

The TAMARA study was an open-label trial involving patients from 70 sites, all of whom received TCZ 8 mg/kg every four weeks. The aim of the study was to confirm the safety and effectiveness of IL-6 inhibition in a diverse population of patients managed in real-life medical settings. Patients had a mean baseline DAS28 of 7.7. Systemic corticosteroids, NSAIDs and other DMARDs were allowed during the 24-week study. With low disease activity as the primary end point, some 52% of the cohort had a moderate EULAR response rate at week 4, while approximately 10% had achieved a good response. At week 24, 37% of patients had achieved a moderate EULAR response while 31% had achieved a good response. Indeed, more than 30% of the cohort had achieved the primary end point of low disease activity (DAS28 ≤3.2) at week 24. Approximately 60% of patients also achieved a HAQ response at week 4, and 65% by week 24. Mean CRP levels dropped from 26.6 mg/L at baseline to almost normal levels one week after treatment and early improvements were seen for fatigue as well. No additional safety signals were observed beyond those in the clinical trials program.

Questions and answers with Dr. Gerd Burmester, Charité University Hospital, Berlin, Germany

Q: What is important about the TAMARA study that physicians should know about?

A: TAMARA is the first study where TCZ was used in a real-life setting. It's a phase IIIb trial which we started immediately prior to the approval of TCZ in Europe and investigators were not the ones that performed clinical trials but everyday rheumatologists. To our surprise, they put patients with the most active disease into this study, with a DAS28 of 7.7. I'm not aware of any study that has included such highly active patients to start with as this one.

Q: There was a lot of interest in this study here at the meeting. Do you think findings are telling everyday rheumatologists not to be afraid to use TCZ in patients with highly active disease?

A: TCZ is still a drug with a recent history so we have to keep this in mind. But we also need real-life patients to see where this drug fits into daily practice. Based on these data, I don't think we need to be afraid to use TCZ in our own practices for patients with highly active disease.

Long-term Safety and Tolerability of Tocilizumab Treatment in Patients with Rheumatoid Arthritis and a Mean Treatment Duration of 2.4 Years

R.F. van Vollenhoven, D. Siri, R. Furie, J. Krasnow, E. Alecock , R. Alten

Purpose: The safety of tocilizumab (TCZ) as monotherapy or with DMARDs has been demonstrated in patients with rheumatoid arthritis (RA) in phase 3 clinical trials and long-term extension studies. The objective of this analysis was to assess the longer-term safety of TCZ in patients with RA using pooled data from the ongoing long-term extension studies and an ongoing phase 3 trial.

Method: The study population included all patients who received at least 1 dose of TCZ in the 24-week, phase 3 clinical trials (OPTION, AMBITION, RADIATE, TOWARD), in the phase 3 clinical trial (LITHE), in a phase 1 study, or in the ongoing, open-label extension studies (GROWTH95, GROWTH96). Safety data were pooled and analyzed from the time of the initial TCZ exposure to the cutoff date of February 6, 2009.

Results: TCZ was administered to 4009 patients, mean treatment duration was 2.4 years, and total treatment exposure was 9414 patient-years (PY). The rate of withdrawals because of adverse events (AEs) was 5.8/100 PY and was driven by elevated liver enzyme levels, infections, and benign and malignant neoplasms. Overall rate/100 PY of serious AEs was 14.91, of serious infections was 4.7, of deaths was 0.53, and of deaths from infection was 0.13. Rates/100 PY of upper and lower GI perforations were 0.01 for stomach/duodenum, 0.03 for small intestine, 0.02 for appendix, and 0.19 for large intestine. Malignancies occurred at an overall rate of 1.16/100 PY, without excess of any one type. Overall rates/100 PY for myocardial infarction and stroke were 0.25 and 0.19, respectively, and did not increase with TCZ exposure. Total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels increased at week 6 and remained relatively stable over time; 313 (7.8%) patients who initiated lipid-lowering therapy during treatment with TCZ generally responded to treatment without complications. The incidences of ALT and AST elevations >3× the upper limit of normal were 3.6% and 1.4%, respectively, during the first 24 weeks of treatment, and the rates did not increase over time. Transaminase elevations were not associated with clinically apparent hepatitis or hepatic dysfunction.

Conclusion: These results demonstrate that no new safety signals have emerged with prolonged exposure to TCZ. Transaminase elevations were not associated with clinically important events. During longer-term treatment with TCZ (median duration greater than 2.5 years), the risks for AEs and serious AEs were stable over time and laboratory changes could be effectively managed. These data support a favorable benefit/risk ratio for TCZ in patients with moderate to severe RA.

Commentary on abstract 1955

The same data from the TCZ clinical trials program were used to assess long-term safety out to a mean of 2.4 years. Serious AEs occurred at a rate of 14.4 per 100 patient-years, while serious infections occurred at a rate of 4.7 per 100 patient-years; neither the serious AE nor serious infection rate increased over time. Comparable rates among controls were 14.4 for serious AEs and 3.4 for serious infections. Rates of GI perforation were low and in line with rates reported in other databases, and all occurred in patients who had at least one risk factor for GI perforation. Malignancy rates were again low (1.1 per 100 patient-years), as were rates for MI and stroke. LDL-C levels did increase slightly in some patients on initiation of treatment, but so did HDL-C levels and the net effect of lipid changes on CVD risk is thus difficult to assess. Elevations in liver enzymes >3x ULN were 3.6% for ALT and 1.4% for AST and rates did not increase over time. Some liver biopsies were carried out in patients who had elevations in liver enzymes and no serious liver disease was detected.

Questions and answers with Dr. Ronald van Vollenhoven, Karolinska Institute, Stockholm, Sweden

Q: Would you stop TCZ in a patient who develops a non-melanoma skin cancer or other treatable malignancy?

A: Malignancy questions are the hardest to answer because we don't actually know. I think with the new drugs, I would not continue treatment but there are no studies telling us what to do with patients who develop a malignancy on treatment or who have had a malignancy prior to treatment, so we really don't know. Until I have more experience with this drug, I would probably not continue treatment though these decisions need to be made on an individual patient basis.

Q: What was the experience with neutropenia like in the clinical trials program?

A: Neutropenia does occur with treatment but it is mostly grade 1; grades 3 or higher occur in single digit numbers. In Europe, it's recommended that physicians check a patient's neutrophils before starting TCZ, but if they do change on treatment, it happens quickly like changes in LDL-C, and in most cases they are not clinically relevant.

Quantification of Dyslipidemia Among Patients with Rheumatoid Arthritis and Changes Associated with Initiation of Anti-TNF Therapy: A Retrospective Database Analysis

J.R. Curtis, A. John, O. Baser

Purpose: Previous research suggests that onset of rheumatoid arthritis (RA) results in decreased lipid levels. Several small studies have shown that tumor necrosis factor-α inhibitor (TNFi) treatment in RA patients (pts) generally leads to increases in total cholesterol (TC), high-density lipoprotein (HDL), and triglyceride (TG) levels (Choy, 2009). This analysis compared lipid levels in pts with RA and osteoarthritis (OA) [objective 1] and determined lipid level changes in RA patients after initiation of TNFi treatment [objective 2].

Method: We used medical and pharmacy claims and laboratory results from a national commercial administrative claims database. Adults had diagnoses of either RA or OA between April 2005 and March 2008; test results for TC, low-density lipoprotein (LDL), HDL, or TG; and no other inflammatory diseases. For objective 1, baseline was defined as 6 months before lipid test results. For objective 2, pts had at least 1 lipid test before and 1 at least 6 weeks after TNFi initiation; baseline was defined as 6 months before TNFi initiation. Results were stratified by whether patients were already taking lipid-lowering medication (LLM) at the time of TNFi initiation. Propensity score matching [objective 1] and multivariate regression [objectives 1, 2] were used to control for baseline differences between RA and OA pts.

Results: We identified 12,319 RA pts and 29,621 OA pts who met eligibility criteria. The proportion of pts with diagnosed hyperlipidemia was significantly lower for RA than OA (49% vs 57%, P<0.0001). RA (vs OA) pts were younger (54 vs 59 mean years) and had higher mean Charlson Comorbidity Index (1.2 vs 0.5) and Chronic Disease Score (4.5 vs 3.1). Use of baseline LLM was lower in RA pts (27% vs 30%; P <0.0001). After controlling for baseline differences, pts with RA (vs OA) had significantly lower TC and LDL levels (Table); RA (vs OA) pts had lower adjusted mean TC (196 mg/dL vs 201 mg/dL, P<0.0001) and LDL (113 mg/dL vs 117 mg/dL, P<0.0001) values. Among the subgroup of RA pts not taking LLM, we observed small but significant increases after initiation of TNFi in TC (5 mg/dL; P<0.0001), LDL (4 mg/dL; P=0.004), and HDL (1 mg/dL; P=0.02). These changes associated with TNFi initiation were not observed in the subgroup of RA pts already taking LLM.

Conclusion: Results of this real-world analysis indicate that RA pts have lower average lipid levels compared with OA pts. In RA pts, initiation of TNFi therapy reversed this effect and modestly increased lipid levels except in pts already taking LLM. Aggressive management of dyslipidemia and decreasing systemic inflammation with biologic agents may reduce excess cardiovascular disease associated with RA.

Table. Proportion of RA and OA pts in each ATP-III lipid category after propensity score matching

Lipid level mg/dL	RA n=11,053 % of pts	OA n=11,053 % of pts	*P*
Total cholesterol			
Desirable <200	58.1	52.4	<0.0001
Borderline high 200-239	30.5	33.0	0.0001
High ≥240	11.4	14.6	<0.0001
Low-density lipoprotein			
Optimal <100	36.6	31.6	<0.0001
Near optimal/above optimal 100-129	36.6	35.8	0.22
Borderline high 130-159	18.7	22.0	<0.0001
High 160-189	6.1	8.1	<0.0001
Very high ≥190	2.0	2.5	0.01
High-density lipoprotein			
Low <40	10.8	10.3	0.28
Normal 40-59	53.9	56.1	0.0009
High ≥60	35.3	33.6	0.005

Commentary on abstract 1600

Patients with RA tend to have lower lipid levels than the general population, perhaps a reflection of generalized inflammation. Nevertheless, RA patients are still at increased risk for CVD compared with the general population. In this study, Curtis et al. compared lipid levels in RA patients to those with osteoarthritis (OA) and also assessed changes in lipids following anti-TNF initiation. Over 12,000 RA patients and over 29,000 OA patients were included in the analysis. Analyses showed that mean total cholesterol (TC) levels were about 5 mg/dL lower in RA than in OA patients, the difference largely driven by differences in LDL-C levels. Following anti-TNF treatment, patients who were not on a lipid-lowering drug had a mean increase in TC of 5 mg/dL—a 4 mg/dL increase in LDL-C and a 1 mg/dL increase in HDL-C. In contrast, anti-TNF treatment did not alter lipids in patients taking a lipid-lowering drug with the exception of HDL-C which dropped by a mean of 3 mg/dL. Investigators concluded that the known excess CV risk in RA patients was probably not related to more adverse lipid levels alone, although approximately 30% of this particular cohort had suboptimal lipid levels and would be candidates for statin therapy.

Questions and answers with Dr. Jeffrey Curtis, University of Alabama at Birmingham

Q: What do you feel this analysis is telling physicians who treat patients with RA?

A: The main message is that it appears your TC goes up by about 5 points once you start on an anti-TNF agent—almost all of it LDL-C—but that if you are on a statin, there are no or negligible changes in cholesterol levels so you need not worry about lipid changes.

Q: Do you think physicians should put RA patients who are about to start anti-TNF therapy on a statin?

A: I think that might be a reasonable option, given the increase in CVD risk that is observed in RA patients. We looked at that as well and found that according to Adult Treatment Panel national guidelines, about one-third had LDL-C <100 mg/dL (2.6 mmol/L); another third had near optimal LDL-C levels but that left about another third who had undesirable levels of LDL-C. So this analysis suggests that a proportion of RA patients should be considered candidates for a statin based on recommendations for the general population without RA.

Fulfillment of the ACR Response Criteria in Patients Receiving Tocilizumab Is not Influenced by its Direct Effects on the Acute Phase Response (APR)

D. Aletaha, F. Alasti, J S. Smolen

Background: TCZ is a novel biological agent targeting the interleukin-6-receptor. In addition to its significant effects on clinical and radiographic outcomes of RA, TCZ exerts a direct suppression of the hepatic APR via IL-6 receptors on the hepatocellular membrane. The ACR20 response criteria were the primary endpoint of TCZ clinical trials, and include APR improvement as an optional criterion. It is unclear how the direct effects of TCZ on the APR influence a patient's ability to achieve an ACR20 response.

Purpose: To assess the relevance of APR for the achievement of ACR20 response in patients with active disease despite MTX or other DMARD therapy in clinical trials of TCZ + MTX when compared to the ATTRACT trial on infliximab (INF) + MTX.

Method: We obtained a random 80% of patient level data from 3 TCZ clinical trials on patients with active disease despite MTX or other DMARD therapy (LITHE, OPTION, TOWARD), pooled the 8mg/kg TCZ arms, and evaluated the presence of the ACR20 response at trial endpoints (6 months; n=919). The ACR20 response requires 20% improvement of both tender and swollen joints (SJC, TJC) and improvement of 3 of 5 additional variables: APR (ESR or CRP), patient and evaluator global assessment of disease activity (PGA, EGA), pain, and physical function. Thus all variables other than joint counts are optional as long as 3/5 are fulfilled. We evaluated whether there was a difference in APR representation among the fraction of patients who just fulfilled 3/5 of the optional criteria (patients with 4/5 or 5/5 criteria. would have fulfilled the criteria in any way). We compared these to the results of a similar analysis obtained in an 80% sample of the ATTRACT trial on INF+MTX in established RA (n=211 at 6 months). All analyses were based on completers.

Results: In the TCZ studies and in ATTRACT, the ACR20 response rate at 6 months was ~68% (Table). In only 10.5% and 14.7%, respectively, of ACR20 responders, this response was attained by just fulfilling 3/5 optional criteria. In total, the fraction of patients, in whom the response in APR qualified for the ACR20 response was similar in the TCZ and INF trials, and amounted to 10% and 11%, respectively (Table).

Conclusion: The APR response was crucial for achieving an ACR20 response in only 10% of patients regardless of treatment regimen.

Table. Rates of ACR 20 responses, frequency of fulfilment of additional variables (3/5, 4/5, or 5/5), and frequencies of variables among patients fulfilling only 3/5 additional variables (i.e. variables were crucial for response classification) for patients treated with TCZ (n=919) or INF (n=211).

		Tocilizumab	Infliximab
ACR20 response	**N (%)**	**622 (67.7%)**	**143 (67.8%)**
Number of optional variables	>3/5 (%)	557 (89.5%)	122 (85.4%)
	=3/5 (%)	65 (10.5%)	21 (14.7%)
Measures improved among patients fulfilling 3 of 5 of the additional variables (% of all ACR20 responders)	APR	61 (9.8%)	16 (11.2%)
	HAQ	27 (4.3%)	11 (7.7%)
	PAIN	24 (3.9%)	10 (7.0%)
	PGA	25 (4.0%)	6 (4.2%)
	EGA	58 (9.3%)	20 (14.0%)

Commentary on abstract 727

Inhibition of the IL-6 receptor not only beneficially affects symptoms, radiographic progression and physical function in RA, it also inhibits activation of the APR in the liver. However, whether this effect contributes to or facilitates fulfilment of ACR response criteria is not clear. This study assessed the relevance of the APR treatment effect for achievement of an ACR20 response. The ACR20 response requires a 20% improvement in both tender and swollen joints, as well as improvement in three of five additional variables. Comparing ACR20 responses in patients treated with infliximab in the ATTRACT trial to those achieved among IL-6 receptor antagonist patients, just 10.5% of TCZ responders vs. 19.7% of infliximab responders achieved an ACR20 response by fulfilling three out of five additional optional criteria. Some 64.3% of TCZ responders and 45.3% of infliximab responders achieved five out of five additional variables, while 25.2% and 35% of TCZ and infliximab responders, respectively, achieved four out of five variables. Thus, almost 90% of ACR20 responders treated with IL-6 inhibition and some 80% of responders treated with infliximab fulfilled more than three of five optional criteria and so did not specifically require a reduction in APR to achieve this response.

Questions and answers with Prof. Josef Smolen, Medical University of Vienna, Austria

Q: What exactly were you assessing in this particular analysis?

A: In this particular analysis, we assessed whether or not it is primarily the effect of the compound on APR such as CRP which leads to ACR responses or if other aspects are also affected. And the study shows that if you achieve an ACR20 response, then the critical item is when patients fulfil three out of five additional criteria, because if you achieve three out of five criteria, it means that one of them may have to be CRP.

Q: But you found only a small proportion of TCZ responders fulfilled only three out of five additional criteria.

A: Yes, we found the vast majority of patients fulfilled either four out of five or five out of five rules for additional ACR20 response criteria aside from improvement in swollen and tender joints, irrespective of reduction of CRP. So only 10% need CRP to be fulfilled to attain an ACR20 response and that number was similar to those treated with a TNF inhibitor, so it's not TCZ's effect on the APR that leads to the ACR20 response.

The Comparative Effectiveness of Biologic Therapies Versus Traditional DMARDs for Fatigue in Rheumatoid Arthritis - A Systematic Review of Clinical Trials

R.C.J. Campbell, G.H. Kingsley, D.L. Scott

Purpose: The OMERACT initiative have considered the appropriateness of fatigue as an outcome measure in RA and recently concluded was that, where relevant, fatigue should be measured in RA clinical trials. Recent studies, largely investigating effectiveness of newer biologic therapies, have been including fatigue as an outcome. Here, the comparative effectiveness of biological therapies versus traditional DMARDs is compared across clinical trials.

Method: Original clinical trials limited to English language were retrieved using MEDLINE, EMBASE and The Cochrane Library through the OVID gateway and analysis of retrieved bibliographies. The 'population' was RA patients. The 'intervention' was anti-rheumatic drugs exploded to include therapies used in routine clinical practise. These were combined with terms fatigue, tiredness and lassitude. Other search terms included were FACIT-F and SF-36. A quality checklist was employed to check studies against 6 specific quality criteria. Studies were ranked according to this checklist and size of study. All identified studies were analysed for therapeutic approaches, type of fatigue data collected, length of intervention and mean change in fatigue. Data were presented narratively and also graphically, where possible, for each fatigue scale. Mean differences for FACIT-F, SF36 and Fatigue VAS weighted for number of study participants were calculated for the RCTs only (extension studies were excluded from this analysis).

Results: 16 clinical trials were identified (9 RCTs, 3 extension studies and 3 observational studies). All RCTs were considered to be of high quality. Of 6 quality criteria, 7 studies fulfilled all and 2 fulfilled all but one criterion. 6 different types of outcomes for fatigue were used altogether. FACIT-F was the most common. Intervention periods ranged from 8 weeks to 52 weeks (3 years for the longest extension study). All 9 RCTs compared fatigue between biologic therapies and standard DMARD therapies. All of the 12 primary trials except one found that mean fatigue reduced most in the biological treatment arm. Mean differences in mean change in fatigue (weighted for number of study participants) between biological and control arms for FACIT F was 3.41, SF36 was 4.14 and fatigue VAS 15.8mm (all in favour of biological treatment arms).

Conclusion: This study suggests that biological therapies reduce RA fatigue more than traditional DMARDs in clinical trials. The one study that does not is cross sectional in design, where treatment followed clinical practise rather than pre- determined protocol. Many of the studies are for relatively short intervention periods (although the few extension studies suggest maintenance of this superiority). Some studies compared newly introduced biologic treatments against established DMARD regimes which, when presenting results regarding change, may be misleading since they do not account for rate of change between these newly introduced and established regimes.

Commentary on abstract 1596

Recent RA trials, mostly involving new biologic therapies, have included fatigue as an evaluable end point, following OMERACT initiative recommendations for its inclusion in overall outcomes. Campbell et al. looked at the comparative effectiveness of biologic therapies vs. traditional DMARDs across a total of 16 clinical trials, nine of them RCTs. The comparison suggested that biologic therapies were associated with less fatigue in RA patients than traditional DMARDs, at least in the setting of a clinical trial. Because the trials did not standardize for other variables that might have had an effect on fatigue, it was not clear from this analysis whether the biologics were associated with less fatigue because they more effectively controlled pain than standard DMARDs. Nevertheless, results showed a definite trend towards the biologics as more effective against fatigue in early if not late RA. The authors also felt that it would be useful to have a consensus as to which tools should preferentially be used to assess fatigue in clinical trials, as a variety of scales are currently used.

Questions and answers with Dr. Richard Campbell, King's College Hospital, London, UK

Q: Is fatigue a reflection of the disease process or the treatments patients are taking for it?

A: Others have shown that fatigue is not necessarily associated with disease activity but there may be other factors such as depression and pain that are causing the fatigue. In early-stage RA, fatigue may be related to disease activity but in the later stages of disease, I don't think it is.

Q: If fatigue is a common and troublesome complaint in RA, would that not argue for early use of the biologics rather than the traditional DMARDs to try and ameliorate the fatigue?

A: I don't think we can say that with certainty. The problem with these studies is that they do not standardize for other effects that might affect fatigue, so you need to do a multivariate analysis to look for these other effects. All we can say is that there is a suggestion that fatigue is improved by biologics but we need further research from a basic science point of view to explain why the biologics affect fatigue, if they do.

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