Advance reports

We report the highlights of two recent meetings, the annual meeting of the European League Against Rheumatism (EULAR), 25–28 May 2011, London, and the annual meeting of the American Society of Clinical Oncology (ASCO), 3–7 June 2011, Chicago.

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EULAR

Etanercept

Several studies on etanercept (Enbrel) were presented at the EULAR congress.

The interim results of the PRESERVE trial[1] were the focus of one of these studies. These results showed that a substantial proportion of patients with moderately active rheumatoid arthritis (RA) receiving a combination of etanercept and methotrexate for 36 months achieved a normal health-related quality of life score (57%), a clinically meaningful improvement in fatigue (73%), and improved sleep adequacy (56%). Investigators Smolen et al concluded: "These outcomes indicate benefits that are consistent with prior studies in different populations (eg, more severe RA) as well as being consistent with clinical and radiographic results from this population." They added that further data from the PRESERVE trial, from the second period of the study, will indicate whether the initial responses observed for patient-reported outcomes are maintained after the dose of etanercept is removed or reduced.

Another study[2] showed that patients with very early stage or early stage rheumatoid arthritis who were treated with methotrexate and etanercept had a higher probability of achieving remission and one or no swollen joints after a year than patients, at the same disease stages, treated with methotrexate alone. Clinical remission with the combination of etanercept and methotrexate was achieved despite stricter criteria from EULAR regarding the definition of clinical remission (achievement of no or one swollen joints and a simplified disease activity score).

Other studies presented on etanercept at the EULAR congress showed: that compared with sulfasalazine, it improved functionality independently of its effects on mobility in patients with ankylosing spondylitis;[3] and that it had greater effect on quality of life in patients with psoriasis and psoriatic arthritis than in patients with psoriasis alone.[4]

Regarding the data presented at EULAR, the Senior Vice President of Clinical Development and Medical Affairs at Pfizer, who are the manufacturers of etanercept, said: "With its first approval for RA in 1998 in the US and 2000 in Europe, Enbrel has 2·5 million patient-years of collective clinical experience, and we continue to gain important knowledge about these conditions and the potential benefits of treating patients with certain chronic inflammatory diseases."

References

1. Poster THU0245, EULAR 2011
2. Abstract AB0439, EULAR 2011
3. Poster THU0488. EULAR 2011
4. PosterTHU0191. EULAR 2011

Studies sponsored by Pfizer

Certolizumab pegol

Adding certolizumab pegol (Cimzia) to current therapy for patients with rheumatoid arthritis was associated with a rapid and consistent clinical response in a study presented at EULAR.[1] The results were from the latest analysis of the REALISTIC study.

In the overall study population, the ACR20 response rates at week 12 were statistically higher in the group of patients receiving certolizumab than in those receiving placebo (51·1% versus 25·9%, respectively). The response rate with certolizumab did not significantly differ between patients who had previously received TNF inhibitors and those who had not (47·2% and 53·5%, respectively).

There also was no significant difference in response rates between those who were receiving certolizumab monotherapy and those who were receiving concomitant disease-modifying antirheumatic drugs (DMARs); 47·6% and 52%, respectively. Other benefits observed with certolizumab included improvements in fatigue, sleep problems, and pain.

Professor Roy Fleischmann, from the University of Texas Southwestern Medical School, said: "These results are encouraging because they demonstrate the clinical usefulness of certolizumab pegol in a broad population of patients with RA and reflect the patient variability that we see in everyday practice."

References

1. Poster FRI024, EULAR 2011

Trial sponsored by UCB

Tocilizumab

Tocilizumab (RoActemra) monotherapy is as effective as tocilizumab in combination with methotrexate in people with rheumatoid arthritis, a study presented at EULAR shows.[1]

The ACT-RAY study randomised patients with moderate-to-severe rheumatoid arthritis who had an inadequate response to methotrexate to remain on stable-dose methotrexate plus 8 mg tocilizumab or 8 mg tocilizumab plus placebo. After 24 weeks, the DAS28 remission rates for those receiving tocilizumab monotherapy was 35% and 40% for those receiving the combination (a non-significant difference). There was also no significant difference in safety profiles between the two treatment arms. In a previous study, tocilizumab monotherapy was shown to have superiority over methotrexate in standard rheumatoid arthritis parameters at 24 weeks.[2] The first and only biologic therapy to do so

Professor Philip Conaghan, Professor of Musculoskeletal Medicine at the University of Leeds, said about the ACT-RAY results: "This data is very promising for patients who are unable to tolerate methotrexate and could provide a more efficacious alternative to current therapy."

References

1. Abstract OP0020
2. Jones G, et al. *Ann Rheum Dis* 2010; **69**: 88–96

Trial sponsored by Roche

RA and QoL

A research report, presented at EULAR and published in the *Annals of the Rheumatic Diseases*, has revealed the impact of RA on quality of life.[1]

The report surveyed rheumatologists and patients across 21 countries in Europe about the effect of morning stiffness and pain associated with RA on quality of life. It found that stiffness and pain in the morning was a daily occurrence for six in 10 of the patients in the survey (to be eligible for the survey, patients had to experience these symptoms at least three times a week). Three quarters of the patients who had daily symptoms rated their symptoms as being at the higher end of the scale (asked to describe the severity of their symptoms on a scale of 0–10, they said their symptoms were at level five or above). Words used to describe morning symptoms included: sore (53%), tired (56%), swollen (58%), restricted (56%), inflamed (45%), and frozen (19%).

Overall, 83% of patients claimed that their symptoms had a significant impact on their quality of life. But in the UK, this figure rose to 92%. The reduced quality of life associated with morning symptoms affected patients' emotional wellbeing. According to the survey, half of patients were "frustrated" by their inability to do certain things because of their symptoms, more than a third felt that they were a burden to others, and almost a quarter felt "depressed" about their symptoms.

Nearly all (96%) of the rheumatologists surveyed recognised that morning symptoms had an impact on patients' lives, but 62% did not specifically treat these symptoms. Only one fifth of patients said that their current treatment was completely effective for relieving their morning symptoms and 66% of European rheumatologists agreed that there was a need for new treatments that specifically address stiffness and pain in the morning.

Professor Douglas Veale, Professor of Medicine and Consultant Rheumatologist at St Vincent's University Hospital, Dublin, said that the report showed it was clear that the morning stiffness and pain associated with RA had an "emotional and economic" impact on patients' lives. "We need to ensure these symptoms

are discussed with patients so that any negative impact on their lives is addressed and minimised."

References

1. Understanding the impact of morning stiffness and pain due to rheumatoid arthritis. A European Research Report in 21 countries

The surveys for the report were conducted by an independent research company and funded by Mundipharma, who produce a treatment for RA (Lodotra) that is particularly for those who have morning stiffness.

Gout

An abstract study indicated that febuxostat (Adenuric) 80 mg is an more effective antihyperuricemic agent than the standard treatment allopurinol.

The study was a meta-analysis of randomised controlled trials comparing febuxostat with allopurinol (found via the online medical database Pubmed). It found that overall, febuxostat was superior to allopurinol in achieving the target serum urate level (<6 mg/dl), the primary outcome, at the end of the study. The investigators concluded that febuxostat was equally safe as allopurinol but advised: "Prophylaxis with colchicine is, however, indicated at the start of the therapy due to slightly increased occurrence of gouty flares before two months of therapy [with febuxostat]. Febuxostat would be a better choice in patients with mild-to-moderate renal insufficiency and for those who are intolerant to allopurinol."

References

1. Abstract AB0037. EULAR 2011

ASCO

Metastatic melanoma

As widely reported in the national press, a study simultaneously published in the *New England Journal of Medicine* and presented at ASCO shows that a new drug, vemurafenib, has the potential to be the first significant treatment breakthrough for metastatic melanoma in 30 years.[1]

At present, patients with stage IV melanoma have a poor prognosis and, depending on their substage, only survive for eight to 18 months after diagnosis. Dacarbazine, the standard chemotherapy used to treat metastatic melanoma, is associated with a 7–12% response rate and a median overall survival of 5·6 to 7·8 months.

About 40–60% of cutaneous melanomas are associated with mutations in the BRAF gene. Of these mutations, 90% relate to the BRAF V600E mutation. Vemurafenib is a potent inhibitor of mutated BRAF and has been showed to have marked antitumour effects against melanoma cells lines with the BRAF V600E mutation but not against cells with wild-type BRAF.

In the study, patients with previously untreated, unresectable stage IIIC or IV melanoma and who tested positive for the BRAF V600E mutation were randomised to receive vemurafenib (at 960 mg twice daily orally) or dacarbazine (at 1000 mg per square metre of body-surface area by intravenous infusion every three weeks). After six months, overall survival in patients receiving vemurafenib was 84% compared with 64% of patients receiving darcarbazine.This equated to a 63% relative reduction in the risk of death in patients receiving the new drug compared those receiving dacarbazine.

Progression-free survival was also better in the vemurafenib group. The estimated median progression-free survival was 5·3 months for patients taking vemurafenib and 1·6 months for patients taking dacarbazine. This equated to a 74% relative risk reduction in tumour progression with vemurafenib. Furthermore, 48% of patients receiving vemurafenib met the criteria for a confirmed response compared with only 5% of patients taking dacarbazine (slightly lower than reported in other studies).

Investigators Chapman et al explained that one of the reasons for conducting the study was that recent studies had raised the possibility that melanomas with the BRAF V600E mutation were more aggressive and less sensitive to chemotherapy than BRAF wild-type melanomas. They concluded: "Our results show that single-agent vemurafenib improved the rates of response and of both progression-free survival and overall survival, as compared with darcarbazine, in patients with metastatic melanoma with BRAF V600E. These findings provide a solid foundation for the development of future combination therapies."

One of the principal investigators of the study, Dr James Larkin, from the Royal Marsden Hospital, said that "without question", the results represented a major turning point in the treatment of metastatic melanoma.

References

1. Chapman P, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Eng J Med* 2011; Epub

Trial supported by Roche

Colorectal cancer

A new study, which was presented at ASCO, has found that adding cetuximab (Erbitux) to standard first-line chemotherapy improves clinical outcome in patients with KRAS wild-type metastatic colorectal cancer who have liver-limited disease or who have non liver-limited disease.

In patients with KRAS wild-type colorectal cancer, the liver is an important area for investigation because resection of colorectcal liver metastases is a potentially curative option. This new study reviewed the treatments arms of the CRYSTAL and OPUS studies (which both showed that adding cetuximab to standard first-line chemotherapy improved clinical benefit in patients with KRAS wild-type metastatic colorectal cancer) according to metastatic site, resection rates, and progression-free and overall survival times.

Investigators found that the addition of cetuximab improved outcome across clinical efficacy endpoints in both patients with liver-limited disease and those with non liver-limited disease. For example in patients with non liver-limited disease, the addition of cetuximab increased overall survival by more than five months compared with standard chemotherapy alone. Also, the rate of potentially curative liver surgery increased by 2–3 fold with the addition of cetuximab in patients with liver-limited disease. However, this increase was not statistically significant.

Mr Giles Toogood, Consultant Hepatobiliary Surgeon at St James's Hospital in Leeds, said: "For most patients with advanced cancer, the chance to live longer, or even be cured, are the most important benefits that treatments can offer." He added that the results were "extremely important" for both patients with liver-limited disease and patients with non liver-limited disease. "We have a strong sign that both groups can benefit from, cetuximab combination therapy."

Trial sponsored by Merck Serono

References

1. Abstract 3576. ASCO 2011

Prostate cancer

A combination of lenalidomide (Revlimid), bevacizumab (Avastin), docetaxel, and prednisone was associated with a high response rate in patients with metastatic castrate resistant prostate cancer in an abstract presented at ASCO.

Prednisone and docetaxel are already established as effective treatments for metastatic prostate cancer. In a previous study, Huang et al hypothesised that the addition of lenalidomide and bevacizumab could improve overall survival in this patient population. Therefore, in this study, they investigated a cycle of treatments involving all four therapies. They found that the combination was associated with an overall response rate of 86·4% and that all responding patients had at least a 50% reduction in prostate specific antigen (PSA). The results were achieved with manageable toxicity.

References

1. Abstract 4574. ASCO 2011

Study sponsored by Celgene

Renal cell carcinoma

Axitinib significantly extends progression free survival in patients with previously treated advanced renal cell carcinoma compared with sorafenib, a new study has shown.[1]

The study assessed 723 patients with clear-cell advanced renal cell carcinoma who had progressed following prior therapy with regimens containing sunitinib, cytokines, bevacizumab or temsirolimus. Patients were randomised to receive axitinib (at a starting dose of 5 mg twice daily) or sorafenib (400 mg twice daily). Compared with patients receiving sorafenib, patients receiving axitinib had a 43% improvement in median progression-free survival. A principal investigator of the study, Dr Brian Rini, said that the data were useful because they helped doctors to advance their understanding of renal cell carcinoma, which has limited proven treatment options when the patient has been previously treated. "The clinically meaningful improvement in progression-free survival seen with axitinib is even more encouraging as it was accompanied by generally manageable tolerability, an important consideration for these patients."

References

1. Abstract 4503, ASCO 2011

Trial sponsored by Pfizer