Randomized Double-Blind Comparative Effectiveness in RA Patients with Active Disease Despite Methotrexate (MTX): A Comparison of Conventional Disease-Modifying Anti-Rheumatic Drugs with a Biologics.


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Abstract

Background: Double-blind placebo controlled trials have demonstrated the efficacy of 15 different disease-modifying antirheumatic drugs (DMARDs), corticosteroids, and biologics. The knowledge to translate these biologicals is substantially more expensive than conventional therapy and not as efficacious. Observational evidence has been accumulating supporting the use of biologicals in suboptimal responders but evidence from randomized, placebo-controlled trials is lacking.

Methods: This investigator-initiated multinational double-blind non-inferiority trial randomized 353 patients requiring a switch in 24 weeks was nearly identical (27.0% for triple and 26.7% for etanercept). Patients were randomized to triple therapy (MTX, sulfasalazine and HCQ) or etanercept and followed for 48 weeks. The primary end point was DAS28 improvement at wk 48 based on either treatment strategy, and results in similar disease measures, function and radiographic progression. At the health system level, the cost-effectiveness of the strategy of starting with conventional DMARD and etanercept is $10,200 per patient year.

Results: Thirty patients baseline characteristics: mean age 57 yrs, 54% males, DAS28 = 5.8, disease duration = 12.3 yrs, and 95% were MTX naive. At baseline there were no differences between groups at baseline. Both groups improved significantly over 24 weeks (p=0.001). The proportion of patients requiring a switch at 24 weeks was nearly identical (27.0% for triple and 26.7% for etanercept). Patients who switched, both groups improved significantly (p <0.0001) and the response was not different between therapies (p=0.08). At 48 wks the change in DAS28 was virtually the same based on the initial randomization (-2.1 [triple] and -2.3 [etanercept]). Importantly, for patients in either group who had responded at wk 24 (73% of the patients) the response was maintained at 48 wks. Radiographic progression was minimal and not different between groups (+ 0.54 for triple vs + 0.29 for etanercept, p=0.43). Secondary patient-reported outcomes HAQII, pain, EQ-5D were also not different. Comparing the direct medication costs of the two strategies, the difference of the drug costs alone between triple therapy and etanercept is $10,200 per patient year.

Conclusions

The strategy of starting conventional combination therapy (MTX, sulfasalazine and HCQ) or etanercept in patients with active disease despite MTX followed by switch to the other therapy when clinically indicated.

Summary

• In MTX suboptimal responders the strategy (T) of first adding SSA and HCQ is non-inferior to first adding etanercept (Δ DAS 28) -2.12 (T) vs. -2.29 (E) (p<0.0001)
• Starting T first was not different radiographically (mTSS) +0.54 (T) vs. +0.29 (E); (p=0.43)
• The switch rate was 27% for both strategies
• Patients improved significantly after a switch from either therapy (p<0.0001).

Conclusions

• The strategy of starting conventional combinations first before etanercept has been validated.
• The efficacy of triple therapy after failure of MTX etanercept and vice versa has been demonstrated for the first time
• The cost implications of these findings are substantial.

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