

# An Investigation into Rheumatoid Arthritis Comparators and Subpopulations

**Context Matters**  
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## OBJECTIVE

To investigate health technology assessments (HTAs) for rheumatoid arthritis (RA) drugs, tumor necrosis factor (TNF) drugs, and disease-modifying, anti-rheumatic drugs (DMARDs), and their comparators to determine how the HTA decisions correlate with subpopulations and RA severity. This association makes an important contribution to the understanding of market entry.

## METHODS

This study analyzes NICE, HAS, IQWiG, HIS, and SMC HTAs published from 2005-2014. (The G-BA, IQWiG's counterpart, did not review RA during this time frame.) These HTAs represent all of the RA HTAs published by these agencies during this time period. (HAS HTAs include only those published in English by the agency.) Ten drugs had HTAs during this time period, for a total of 77 reviews.<sup>1</sup> (A review is considered a single drug/indication item reviewed by an HTA. Because some agencies combine multiple drugs, indications, and subpopulations into a single assessment, one assessment may result in multiple reviews.) Eight drugs were reviewed 75 times; only two drugs and reviews were for non-biologics. The indication under review by the HTA body was categorized for severity and into the following, non-mutually exclusive indication segments: DMARD-inadequate response (IR) or intolerance, TNF-IR or intolerance, methotrexate-naïve, and methotrexate-IR or intolerance. Severity was defined as Moderate-to-severe, Severe, and Unspecified. Comparators were categorized into two non-mutually exclusive segments: comparators that included biologics and comparators that included methotrexate.

## RESULTS

The comparator was not reported in 17 reviews. Methotrexate (either alone or in combination) was used as the comparator in 48 reviews; 21 reviews used methotrexate exclusively as a comparator; and 27 reviews used the newer biologic drugs (five alone, and 22 in combination with methotrexate). Severe RA was reviewed 30 times and used biologics as comparators only six times; in each of those, the comparator biologic was in combination with methotrexate. Three reviews used methotrexate in combination with rituximab, a low-cost biologic; one used a new biologic in the combination; and two did not specify which biologic was the comparator. Infliximab was specified as a comparator six times; in each case, it was compared to abatacept when reviewed for moderate-to-severe RA. Infliximab, in combination with methotrexate, now has two biosimilar products on the market in the EU. (At the time of the analysis, the two SMC reviews for biosimilar infliximab were not yet published.)

## CONCLUSIONS

Severe RA was reviewed 30 times, but usually not using biologic drugs as the comparators. Since all severe RA drugs in these reviews are biologics, it appears that the clinical hurdle for RA is low. Moreover, a second barrier may emerge to clinical trials in moderate-to-severe RA when biosimilar infliximab is reviewed by HTAs in the EU.

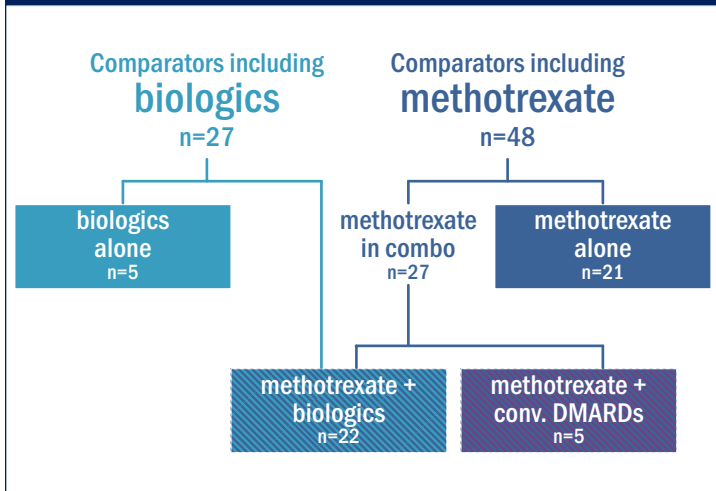
1. The data were sourced from the Context Matters database and included RA reviews published in English by NICE, SMC, HIS, HAS, and IQWiG from 2005 to 2014.

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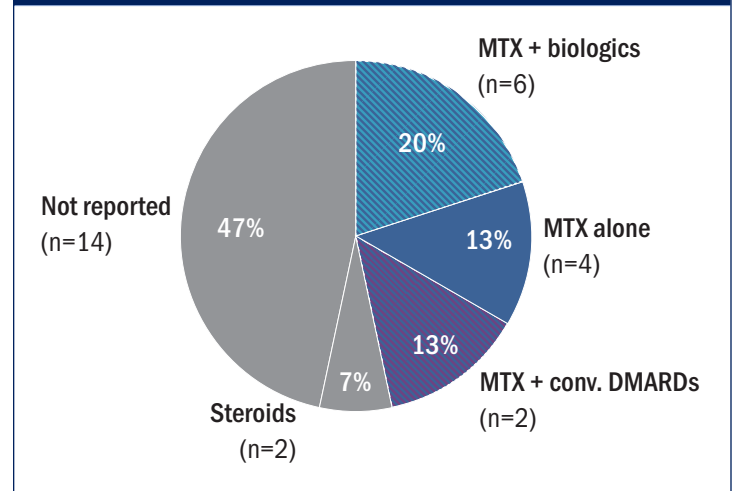
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## RA Comparator Types



## Severe RA Comparator Breakdown



## Use of RA Comparators and Subpopulations

Comparators	Subpopulations				RA Severity		
	DMARD-intolerant	TNF-intolerant	methotrexate-intolerant	methotrexate-naïve	Moderate-to-severe	Severe	Unspecified
Biologics alone	3	3	1	0	3	0	2
Methotrexate + biologics	21	15	8	2	13	6	3
Methotrexate alone	8	2	8	1	6	4	11
Methotrexate + conventional DMARDs	0	0	0	0	0	4	1
Other <sup>†</sup>	4	4	1	0	2	2	3
Not reported	13	11	11	6	2	14	1
<b>Using biologics</b>	<b>24*</b>	<b>18*</b>	<b>9</b>	<b>2</b>	<b>16</b>	<b>6</b>	<b>5</b>
<b>Using methotrexate</b>	<b>29</b>	<b>17</b>	<b>16</b>	<b>3*</b>	<b>19</b>	<b>14</b>	<b>15</b>

\* p<0.05 measured by Fisher's exact test

<sup>†</sup> Other includes placebo (n=4), steroids (n=2), and conventional DMARDs (n=1).