Screening for TNF response prior to initiation of biologic therapy for precise targeted therapy

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DNP Quality Improvement Project

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Abstract

Objective: A quality improvement project to improve outcomes in rheumatoid arthritis (RA) patients who are anti-CCP positive by starting targeted biologic/targeted synthetic DMARDs (b/tsDMARDs) therapy after screening for tumor necrosis factor inhibitor (TNFi) response. Using a targeted therapy approach, patient's disease activity was checked before and after intervention. The goal was to achieve a clinical disease activity index (CDAI) of <10, showing low disease activity. Methods: Quality improvement model used was the Plan-Do-Study-Act cycle to aid in implementing change to improve patient outcomes. Quality improvement project used Lewin's change theory. The project allowed for change in provider behavior and organization by using a systemic approach and strategies to improve patient outcomes. Lewin's change theory consists of three parts: unfreezing, changing, and refreezing. The project unfroze the traditional way of prescribing biologic therapy. The screening tool for TNFi response was the change used to find TNF inhibitor non-responders prior to or during biologic therapy. The refreezing part of the theory is to continue screening for TNFi response after the project to ensure the most proper biologic is chosen. Results: A total of 27 patients were screened with TNFi non-response prediction tool during a 6-week period. 10 patients were predicted non-responders to TNFi therapy. 15 patients had no prediction of non-response to TNF inhibitor therapy. Two patients were not resulted due sample quality issues. Test results information, the patient's clinical picture, and therapies were adjusted accordingly. Conclusion: The use of the TNFi non-response prediction screening tool allowed for the 10 predicted non-responders to avoid TNFi that would be traditionally started on first line treatment. These 10 patients saved time, money, health, disability, and joint deterioration by starting or continuing proper treatment.

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Rheumatoid arthritis (RA) is a significant problem effecting a broad patient spectrum from ranging from pediatric to the geriatric population. Although RA can appear at any age, it is most likely to present between the ages of 30 to 50 years of age. RA is systemic disease that can affect multiple organs and is the most common autoimmune arthritis. RA affects 1.3 million Americans, and around 75% of RA patients are women (ACR, 2022). It is a chronic inflammatory condition that can affect multiple joints. It results in pain, swelling, and stiffness to the joints affected. Additionally, if uncontrolled the inflammation may lead to irreversible joint damage leading to deformities and disability (Chastek et al., 2017; Kavanaugh et al., 2018).

RA can be subdivided into two types seropositive or negative based on the presents or absence of RA related antibodies. Seropositive patients have either a Rheumatoid Factor (RF) antibodies or Anti-Cyclic Citrullinated Peptide (anti-CCP) antibodies (Whitbourne, 2021). Seronegative patients do not present with either antibody. Anti-CCP antibodies are useful in the diagnosis of RA given they carry high specificity. Anti-CCP antibodies are present in early development of disease and show those likely to develop severe and irreversible joint or organ damage (Niewold et al, 2007).

Treatment modalities consist of conventional Disease Modifying Antirheumatic Drugs (cDMARDs) and Biologic/Targeted Synthetic DMARDs (b/tsDMARDs). Biologic treatments slow disease activity, halt radiographic progression and improve function and quality of life measures (Curtis, 2011).

The American College of Rheumatology (ACR) treatment guidelines support the use of cDMARDs prior to b/tsDMARD therapy. ACR recommends a “treat to target approach” which is

often referred to as low disease activity or remission (Fraenkel et al.,2021). In most cases of anti-CCP RA patients there is often a need for b/tsDMARD therapy due to the aggressiveness of the disease. ACR further recommends for the patient to be at low disease activity within 6 months of diagnosis. This recommendation is to prevent the disease from progressing and causing deformities and disability.

The ACR also uses ACR 20/50/70 score to measure improvement in patients during clinical trials of biologics. The scores reflect a 20%; 50%; 70% improvement in the number of tender and number of swollen joints, and improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure, visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (Felson and Pincus, 2022).

Most b/tsDMARD are used after failure of methotrexate or other cDMARDS. Methotrexate is used as first line treatment unless contraindicated (John Hopkins Medicine, 2022). Methotrexate is low cost, and slow acting. Methotrexate can take 6 months to be fully effective (Murray et al, 2021). Methotrexate used alone as monotherapy does not often reach low disease activity score in about 70-80% of patients (Bello et al, 2017). Other cDMARDS include Leflunomide, Sulfasalazine, Hydroxychloroquine, Azathioprine, and Mycophenolate Mofetil. Like methotrexate, theses cDMARDs do not always control disease activity monotherapy and often need the aid of biologic therapy to stop disease progression and damage. Combination of cDMARD and biologic have various randomized control studies showing that they work better in combination than alone (Benjamin, 2021).

All b/tsDMARDs come in various formats depending on their mechanism of action. Their ability to block certain cytokines distinguishes their classification (Benjamin, 2021). The longest tenured biologic therapy is the TNFi drug line. TNFi therapy has been studied since the

late 70's into the 80's. Early synovial studies concluded that TNF was at the head of a pro-inflammatory cytokine 'cascade' seen in active inflammation (Monaco et al, 2015). The first TNFi was launched in the mid 1990's and have shown considerable evidence of ability to control RA. TNFi are the most studied biologic due to their length of use. TNF inhibitors are started first line therapy 90% of the time after methotrexate, but over one third of those patients do not respond to TNFi (Johnson et al, 2019). Most insurance payer's formulary consists of TNFi therapy first line to treat moderate to severe RA. Often insurances require a second and even third failure of TNF inhibitor therapy before considering a different mechanism of action. This dilemma happens in lieu of ACR recommendations to trial another mechanism of action after failing one TNFi.

A trial-and-error approach to biologic therapy using TNFi is often used to treat patients with anti-CCP RA with moderate to severe disease. Genetic factors such as defective myosin binding can explain reasons why 40% of patients prescribed TNFi do not respond to therapy and finding genetic biomarkers of treatment response is important in deciding efficacy of treatment (Husni, 2020). According to Scipher Medicine, biologic response rates decrease anywhere between 16-35% after failing first biologic. There is an increased use of pain medications and steroids. Up to 83% of joint surgeries are involved with irreversible joint damage and chronic pain when treating with a non-responsive biologic agent (2022). Scipher Medicine developed the PrismRA, a molecular signature response classifier that predicts non-response to TNFis with a 90% positive predictability of response, it has a sensitivity of about 60% and specificity of 77% (Scipher, 2022). The screening tool informs the selection of a targeted therapy approach to aid in achieving disease control and remission. The TNFi non-response prediction tool intends to reduce inappropriate use of TNFi. PrismRA studies showed patients who were predictive non-

responders were 3 to 9 times more likely to fail TNFi then those without a prediction of non-response (Scipher, 2022). Strand et al (2022) confirms that predicted non-responders who are prescribed biologics other than TNFi showed a significant improvement in therapeutic response. The studies further showed that approximately 35% of patients obtained improvement in symptoms of up to 50% according to ACR50 using an alternative mechanism of action (alt-MOA), compared to 10% who reached ACR50 on a TNFi while having a non-response predictive screening (Strand et al, 2022). Finally, the study concluded by that 56% of patients achieved desired CDAI score while on alternative mechanism of action compared to 15% on TNF inhibitor therapy with predicted non-response (Strand et al, 2022).

Other biologic agents used as alternatives to TNFi therapies depend on their mechanism of action. They include interleukin 6 (IL-6) inhibitors, t cell inhibitor therapies, b cell modulator therapies and Janus Kinase inhibitor (JAKi) therapy. Most alternative biologic therapies are introduced after TNFi failure. Recent changes to package insert to JAK inhibitor therapy state that the therapy be used after failure of TNF inhibitor therapy. The changes were brought on by long term safety data and post surveillance data (FDA, 2021). The changes were made days prior to initiation of quality improvement project. Prior to changes, JAK inhibitor therapy could be used first line if needed.

The quality improvement project allowed for screening of RA patients who are anti-CCP antibodies positive with TNF inhibitor response tool. The TNFi prediction on non-response screening tool results are as follows; No Signal: meaning there was no signal predicting non-response to TNFi, but this does not indicate a likelihood of response; High Non-Response: showing likelihood of not responding to TNF inhibitor therapy, and Very High Non-Response: showing about a 95% chance of no response to TNF inhibitor therapy (Scipher, 2022). The

patients screened were both biologic naïve and on current biologic treatment. Adjustments to biologic therapy was guided by TNF inhibitor response.

The project goal was to screen patients with TNFi non-response prediction tool and with predicted therapy, target low disease activity within the given timeline. Unfortunately, most b/tsDMARDs can take 3-6 months to find full response. One key factor of JAKi therapy is that most have a fast response, as well as efficacy as monotherapy (Westhovens, 2019). The rapid onset of JAKi allowed for evaluation in CDAI scores during project timeline. The project timeline limited normal standard of practice used to evaluate efficacy. The project proved helpful in finding responders from non-responders to anti TNF inhibitor therapy and guidance to targeted therapy approach.

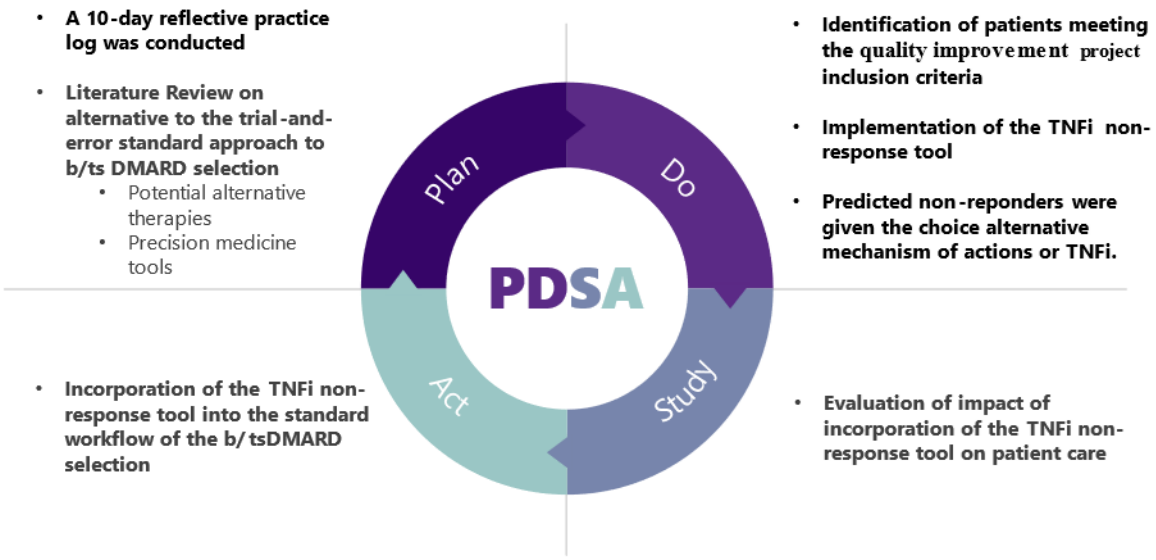
Methods

The quality improvement project took place during Jan 17, 2022, through February 25, 2022. Patients were evaluated at Texas Arthritis Center clinic in El Paso, TX.

Model

The quality improvement model used the plan-do-study-act (PDSA) cycle. The PDSA model of improvement focuses on improving patient outcomes **(Figure 1).**

Figure 1



PDSA- PLAN: This phase of the cycle took place at the project site. A 10-day reflective practice log was conducted and showed inadequate control of symptoms on TNF inhibitor therapy in randomly selected patients. Inadequate control of their disease meant that patients continued to deteriorate, and their disease progressed while on biologic therapy. Rather than use a trial-and-error approach in guiding the next treatment choice, a literature review was conducted to recognize potential alternative therapies that were equal or superior to TNFi therapy.

PDSA- DO: To be included in the DO portion of quality improvement project the patients had to meet the following eligibility criteria. These patients were adults between the age of 18 -80 with a clinical diagnosis RA. There were currently being treated at the Texas Arthritis Center clinic in El Paso and experiencing activity disease symptoms and have positive anti-CCP lab test result. All patients had a history of methotrexate treatment or other cDMARD treatment. Those patients meeting the eligibility criteria started on the intervention protocol and move through the last to phase of the PDSA cycle.

The intervention employed the use of a TNFi non-response prediction tool. TNFi non-response prediction tool (commercially available as PrismRA® Scipher Medicine, Waltham, MA), involved a onetime blood draw sent for analysis. Test results were available about one week post request. All patients meeting the eligibility criteria were screened with the TNFi non-response prediction tool. Once screened, results were discussed with the patient. For the patients who were predicted non-responders to TNFi therapy the following options were presented; for established patients on TNFi who were predicted non-responders they could choice to change therapy to alternative mechanism of action or continue with no treatment changes. For new patients screened who were ready to advance to a b/tsDMARD therapy were given the option to advance to an alternative mechanism of action such as a JAKi, rather than traditional first line therapy of TNFi. All treatment options were discussed thoroughly per manufactures packet insert.

PDSA- STUDY: The impact of the intervention was evaluated by determining how the TNFi non-response tool test results shifted the use of TNFi in this cohort. Secondly, the patient's clinical response to therapy within last 4-6 weeks of the project timeline. For some patients, the restrictive timeline of the project did not allow for complete clinical follow-up. Data was collected at initial visit and at follow up visits. The data collected consisted of clinical assessments, RA medical history, routine laboratory testing, TNFi non-response prediction tool test.

The Clinical Disease Activity Index (CDAI) used to evaluate the level of patient's RA disease activity. CDAI measures the count of swollen and tenderness of 28 specific joints along with patient and physician global scores to estimate disease activity (Singh et al., 2011). The ranges are from 0-2.8 shows clinical remission, >2.8- 10 shows low disease activity, and >10-22

shows moderate disease activity, and finally >22-76 shows high disease activity (Medscape, 2020). CDAI prior to TNFi response screening tool showed moderate disease activity (mean CDAI 19) in no signal predictive non-responding group. The predicted non-responding group showed high disease activity prior to screening (mean CDAI 24).

PDSA- ACT: The ACT phase of the PDSA cycle allowed for continuation of intervention for future purposes. The screening for TNFi non-response tool accommodates for better patient outcomes. Continuing to use the tool will enable providers to select the most appropriate b/tsDMARD therapy for patients.

Intervention

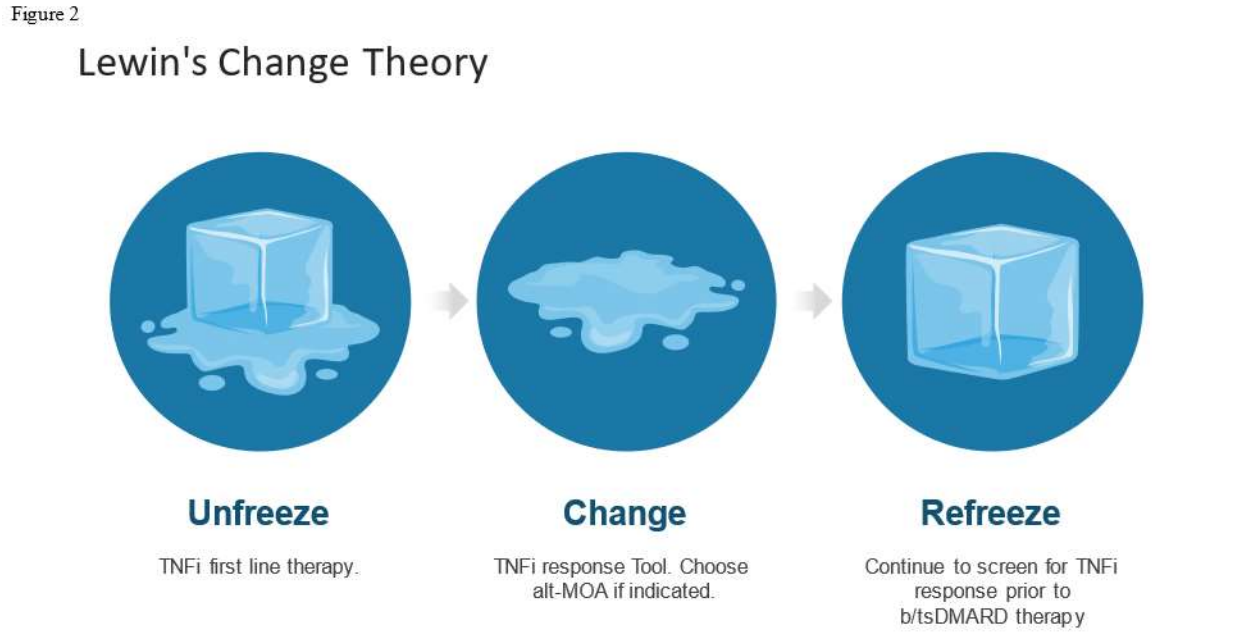
TNFi non-response prediction tool or TNFi response screening tool integrates disease-associated RNA transcripts, and clinical features (anti-cyclic citrullinated protein, sex, body mass index, patient disease assessment) is validated to predict the likelihood that an individual RA patient will be a non-responder to TNFi therapy (Cohen et al., 2021). The test algorithm generates a score on a continuous scale of one to 25: the higher the score the greater the likelihood of non-response to all TNFi therapies (Strand et al., 2022). Patients with a score ≥10.6 are predicted non-responders to TNFi. Those patients with a score <10.6 are not predicted non-responders however, this does not ensure that they will be responders to TNFi as the test was not developed to predict response to TNFi therapy.

Framework

The project used Lewin's Change Theory to implement meaningful change into standard practice. The intentions of the framework were to disrupt the status quo presented by initiation of TNFi therapy first line. The project used three phases of the theory to implement a new standard of care. The phases are unfreezing, changing and refreezing.

The steps address the need for change by finding what is needed to change (unfreezing), the intervention is implemented (changing) and provides new advances to care while improving patient outcomes. The refreezing part reflect changes that will need to be reinforced by continuing to screen for TNFi response. The refreezing phase allows for integrating and stabilizing a new equilibrium, so it becomes the norm and does not change (Wojciechowski et al, 2016). In the future the TNFi screenings will be done prior to biologic use to choose the best targeted approach (**Figure2**).

Figure 2



Ethical considerations

Patients that took part in the quality improvement project were informed of the screening tool and the significance of the tool and how it may help guide their therapy. All patients volunteered to take part in the project. The screening tool was not charged to their insurance. Samples of the screening tool were used for all patients. The patients were informed on purpose of the tool and agreed verbally to follow up at their designated time. The tool reported that

patient's likelihood of not responding to TNFi therapy or no-signal of non-response was detected. The decision to advance therapy was still up to the patient's discretion after risks and benefits were discussed. The standard of care is "treat to target" approach as per ACR recommendations. The target is low disease activity or remission. The use of biologics is often needed to achieve desired outcomes in patients with anti-CCP RA. There are risks associated with biologic therapies, as per manufacturer, of both TNFi and JAKi therapies. Safety between the two options is comparable (Fleischmann, R. et al., 2019). The benefits outweigh risks considering debilitating disease if no treatment chosen. Patients were given the option to try b/tsDMARD therapy once risks and side effects had been explained for each treatment option. All patients had the right to refuse treatment.

Results

PDSA- PLAN

A 10-day reflective practice log showed inadequate control of symptoms on TNF inhibitor therapy in randomly selected patients. The unfreeze proportion of the Lewin's Change Theory was supported by a literature review of alternative mechanisms action drug to TNFi. An estimated 90% of RA patients are prescribed tumor necrosis factor inhibitor (TNFi) therapies, the world's largest selling drug class (Curtis et al., 2017). An independent meta-analysis of published randomized controlled trials found that TNFi having a 50% response by the American College of Rheumatology (ACR) response criteria (ACR50) at 6 months ranged between 27.1% and 37.5% (Incerti, 2018). A literature review of JAKi therapy published studies show a variance in the clinical outcomes where some reported clinical findings equally, if not more effective at treating RA than TNF inhibitor therapy (Sung & Lee, 2021)). During the Select Compare trial a JAKi therapy (Upadacitinib) in combination with methotrexate was superior to a TNFi and placebo

(Fleischmann, R. et al., 2019). The Oral Strategy trial also showed non inferiority of a JAKi (Tofacitinib) and methotrexate versus TNFi and methotrexate (Fleischmann, R. et al., 2017). A third JAKi (Baricitinib) therapy demonstrating non-inferiority in comparison to a TNFi, although dose used for JAKi is not FDA approved in the United States (Taylor, P. et al., 2017). Other therapies also noted to be superior or equal to TNF inhibitor therapy are IL-6 and T- Cell therapies (Choy et al, 2019; Weinblatt et al, 2013).

Furthermore, it has been reported that the number of prior DMARDs is associated with lower clinical response (Curtis et al., 2014). This underscores the need to be able to appropriately pair the patient with the most biologically correct targeted therapy. Literature review supported that the use of TNFi first line in the majority of patients is a practice norm rather than an action supported by evidence-based practice.

PDSA- DO

27 patients who met eligibility criteria for the intervention part of the quality improvement project and were screened with the TNFi non-response prediction tool. The screened patient demographics are presented in **Table 1**. 21 of the patients screened for TNF response were female and 6 were male. The ages range from 31-70 years of age. The mean age being 56. Ethnicity of patients include 25 patients Hispanics and 2 White. The mean CDAI of all 27 patients prior to TNF response screening was 19 showing moderate disease activity.

Table 1

Demographic Information

	Total	TNF no signal predicted non-responders	TNF predicted non-Responders
Age, mean +/- SD Years	56.3+/-10.7	57+/-9.5	52 +/- 10.9

	Total	TNF no signal predicted non-responders	TNF predicted non-Responders
Sex			
Female	21	10	9
Male	6	5	1
Ethnicity			
Hispanics	25	15	9
White	2	0	1

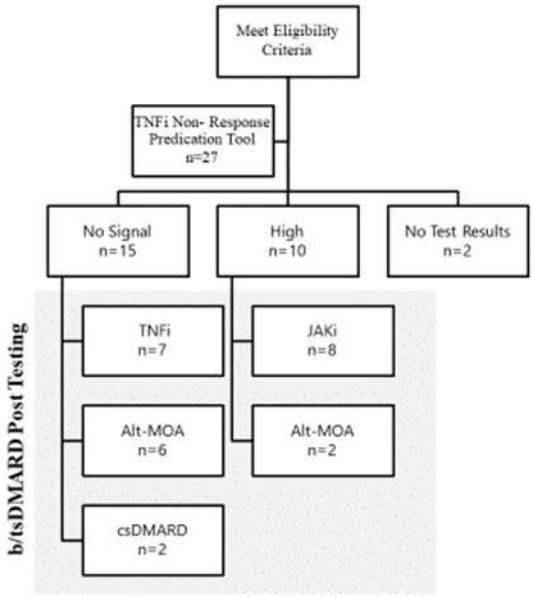
The test results break down fell into three categories, No Signal, High Non-Responders, and Not Test Results (**Figure 3**). 15 patients showed No Signal response indicating no presents of an underlying biological incompatibility with TNFi however, this does not guaranty response to TNFi therapies. 10 patients showed High Non-Responders to TNF inhibitor therapy indicating these patients had a 95% likelihood of not responding to TNFi therapy at an ACR50 level at 6 months (Cohen et al, 2021). 2 patients had Not Test Results; the patient samples failed quality control checks for processing. Patients who were predicted non-responsive to TNFi therapy had previously not done well with TNFi therapy. Also, not all patients who were scored at No Signal had done well on TNFi inhibitors previously. The results coincided with the Scipher data. Scipher reported 60% sensitivity to non-responders of TNF therapy (Scipher, 2022)

In the No Signal detected group of 15 patients; 7 patients started TNFi therapy, 6 alt-MOA therapies and 2 continued on csDMARD therapy (**Figure 3**). The patients on TNFi therapy scheduled in 3 months to assess efficacy. The patients on alt-MOA were also followed clinical and within the timeframe of the project were well controlled. Beyond the project they stayed on their b/tsDMARD therapy and were followed up as part of their routine care. Of the patients who continued cDMARD, one was well controlled with a CDAI of 6 and no advancement to biologic

was necessary. The other had been off cDMARD for months prior to screen, the patient chose to continue previous treatment. Patient's CDAI prior to returning to cDMARDs was 24.

In the High Non-Responders detected group of the 10 patients: 5 of the 10 non-responders were on TNF inhibitor therapy and failing treatment. Four of these patients were biologic naïve and one was on a JAKi at the time of testing. Post testing 7 patients transitioned to JAKi therapy, one patient had their JAKi dose adjusted and 2 were put on non-JAKi alt-MOA therapies (IL-6 and T Cell) due to contraindications (**Figure 3**).

Figure 3



PDSA- STUDY/ACT

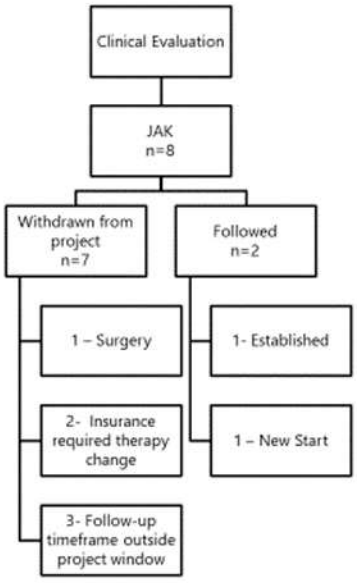
The quality improvement project took place during Jan 17, 2022, through February 25, 2022. This timeframe did impose a restriction on the clinical evaluation period. 2 of the 10 patients with a High Signal and treated with alt-MOA were able to be fully evaluated during the project timeframe. 8 patients were withdrawn from the evaluation period of the project (**Figure 4**). The two patients started on alternative mechanism of action other than JAKi were excluded

from clinical review part of the project. The project timeline would not allow for full evaluation of efficacy of these therapies. One patient was started on JAKi therapy but had surgery prior to follow up and was excluded from project due to interruption in therapy. Two patients were started on a specific JAKi and two weeks into their treatment their insurance informed them that their JAKi was not covered and needed to change to another JAKi that was in their formulary. Due to this process, they were excluded from the project.

Three patients did not keep their scheduled appointment for follow up. These 3 patients showed improvement at their rescheduled follow up, but unfortunately fell after project deadline and were excluded.

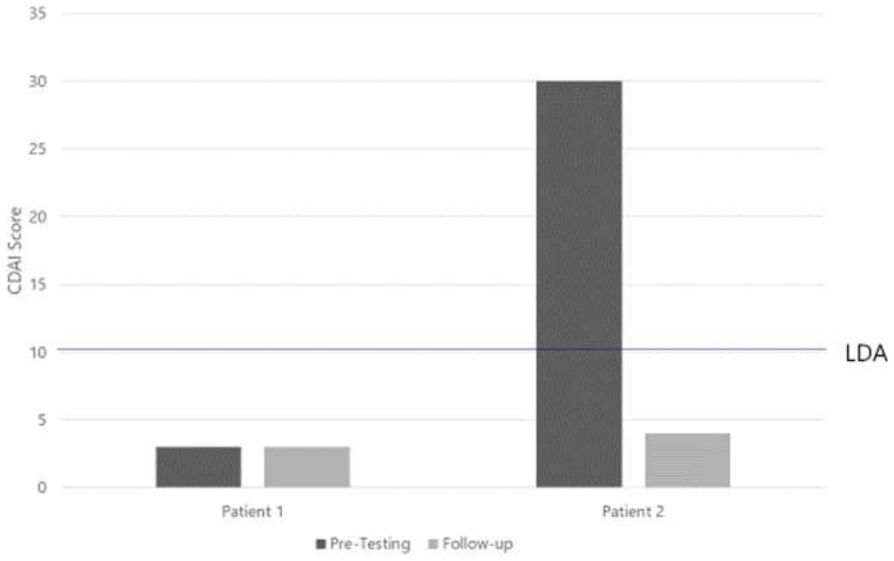
The patient who was already on JAKi therapy was well controlled. The patients CDAI score was 3 indicating low disease activity. Treatment was adjusted due abnormalities on labs but remained on the JAKi.

Figure 4



One patient followed through entire project implementation. Initial CDAI was 30 (high disease activity) and at the 4-week follow-up the patient was at a CDAI of 4 showing low disease activity after initiation of targeted therapy (**Figure 5**). There was a 26-point decrease in disease activity by choosing an alternative mechanism of action when TNF screening tool showed High prediction of non-responds to TNFi. The tsDMARD chosen was also initial targeted therapy.

Figure 5



The project showed responders from non-responders to TNF inhibitor therapy and allowed for targeted biologic approach. Scipher reports more than $552 billion is wasted annually across the healthcare system when patients are prescribed medication they don't respond to, and RA is the largest contributor among autoimmune disease (Arnell, C., 2021). Arnell et al, reported that for predicted non-responders the potential savings ranged from $200,000 to $770,000 by changing to alternative mechanism of action (Arnell, C., 2021). Annual cost savings for the ten non-responders is approximately $60,910 by being on a targeted therapy in comparison to not on targeted therapy (Arnell, C., 2021). Arnell et al., also confirm that

targeted approach using TNFi screening might save the US health care system more than $850 million annually and improve ACR50 by up to 31.3% (Arnell, C., 2021).

Discussion

The TNFi predicted non-response screening tool showed 10 patients who were predicted non-responders to TNFi therapy. They started on targeted approach therapy. Incorporation of a TNFi non-response tool into the clinical decision-making process of b/tsDMARD section could lower healthcare costs, slow disease progression, lower mortality rate, decrease pain, improve function and quality of life by helping patient avoid ineffective drugs. (Scipher, 2022). Predicted therapy will help guide treatment, reduce adverse effects and avoid treatments with drugs without favorable outcomes (Bek, 2017). The screening tool allowed for a targeted approach controlling disease in a matter of weeks compared to what could have taken months to figure an out inadequate response before changing therapies. The average period to assess TNFi failure can take 9-12 months (Scipher, 2022). Precision medicine and targeted approach is a new method of treatment that allows for predicted response to treatments instead of trial and error.

Limitations

Limitations of project include time allotted to implement project. Normally, follow ups are from two to three months to assess response to therapy. Due to quick onset of JAKi therapy the project was able to find improvement in four weeks. Other therapies prescribed usually take longer and more time is needed to assess response. Other limitations include follow up appointments changed or rescheduled by patient. Sufficient data could not be collected, and patients were excluded for not following up. Insurance formularies were a setback on a couple of patients due to prescribed therapy not being in their formulary. Sample size is also a limitation, more patients would of have shown a difference in data giving the project more validity.

Conclusion

The screening tool aided in choosing a targeted approach to treatment versus a trial-and-error approach. Trial and error approach continue in 90% of patients with RA and TNFi therapy (Johnson et al, 2019). The implementation of the TNF inhibitor screening tool prior to b/tsDMARD significantly improves patient outcomes.

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