NP-120 AND NP-178: REPURPOSED NEUROLOGICAL DRUGS WITH EFFICACY IN ANIMAL MODELS OF ULCERATIVE COLITIS AND CROHN'S DISEASE

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Objective

- To determine whether repurposed drugs could reduce inflammation and disease severity in mouse models of inflammatory bowel disease

Introduction

- Ulcerative Colitis (UC) and Crohn's Disease (CD) are chronic inflammatory diseases affecting the colon. In severe cases fibrostenosis can develop, requiring surgery.
- Mild cases of IBD can be treated with aminosalicylates; moderate or severe cases require more effective agents. TNF-blockers predispose patients to serous infections, and biologics are expensive and inconvenient.
- Algernon Pharmaceuticals pursued a drug repurposing strategy, wherein drugs approved outside the USA and Europe, whose long-term safety data was known, were tested for efficacy in animal models of disease.
- Here, we describe the results of two experiments investigating a number of repurposed compounds in oxazolone-induced UC and TNBS-induced CD.[1,2]

Methods

Oxazolone-induced Ulcerative Colitis.

- Healthy female SJL/J mice aged 7-8 weeks, weighing 18-20g were acclimatized for 7 days, then divided into groups of 15 (for treatment) or 10 (treatment naïve)
- Mice were pre-sensitized by injection of 200 µL of 3% (w/v) solution of oxazolone in ethanol once per day for 5 days (treatment naïve group received only ethanol)
- Mice were challenged intra-rectally with 150 µL of 1% oxazolone in 50% ethanol to induce UC
- Treatments were dosed as a solution in DMSO or 0.5% CMC QD for 7 days as follows: 5-ASA - 100 mg/kg; NP-178 - 160 mg/kg; NP-120 - 30 mg/kg
- Body weight, disease activity index (DAI, a composite of body weight, fecal consistency and occult positivity) and mortality were recorded daily
- On termination, surviving animals were sacrificed and the colon removed and cleaned; lengths and weights were recorded
- Colon sections were fixed in formalin, then analyzed histopathologically following H&E staining
- Results were analyzed by two-way ANOVA following a Bonferroni post-test

TNBS-induced Crohn's Disease

- As UC procedure, but with no pre-sensitization period. After 7 days acclimatization, mice were challenged intra-rectally with 100 µL of 2% TNBS in 50% ethanol to induce CD

Results

NP-178 and NP-120 improve Disease Activity Index in mouse models of UC and CD

Fig. 1.1 DAI in UC

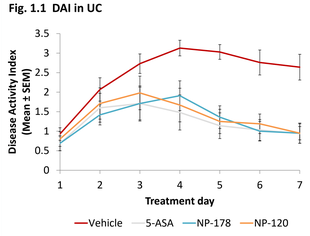
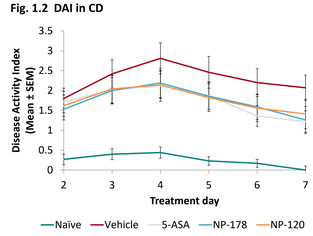


Fig. 1.2 DAI in CD



- In UC, The groups treated with 5-ASA and NP-120 showed significant improvement in DAI as compared to vehicle beginning day 4 and continuing until day 7; NP-178 showed the same effect beginning on day 5. In CD, improvements in the treatment groups vs. vehicle were not significant.

NP-178 and NP-120 reduce mortality in mouse models of UC and CD

Fig. 2.1 Mortality in UC

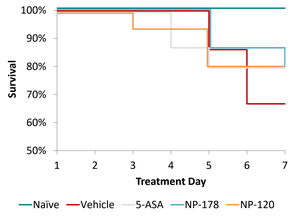
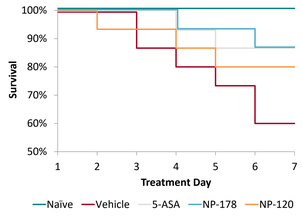


Fig. 2.2 Mortality in CD



- The survival was greatest in the group treated with NP-178, followed by 5-ASA, NP-120 and vehicle. Differences were not statistically significant.

NP-178 and NP-120 improve colon size in mouse models of UC and CD

Fig. 3.1 Colon weight/length ratio in UC

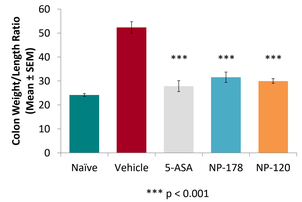
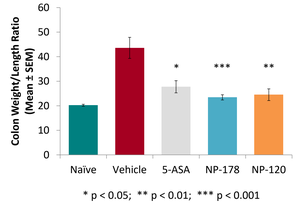


Fig. 3.2 Colon weight/length ratio in CD



- In the UC group, all treatments led to significant reduction in colon weight/length ratio vs. vehicle. In CD, the reduction was greatest in the group treated with NP-178, followed by NP-120 and 5-ASA; differences between treatment groups were not significant.

NP-178 and NP-120 reduce weight loss in mouse models of UC and CD

Fig. 4.1 Body Weight Change in UC

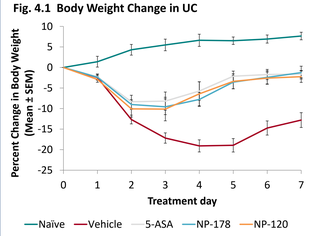
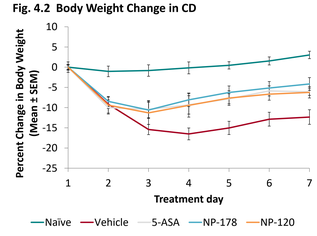


Fig. 4.2 Body Weight Change in CD



- The groups treated with 5-ASA, NP-178 and NP-120 showed significant improvement in body weight gain as compared to vehicle beginning day 4 and continuing until day 7 in both UC and CD.

NP-178 and NP-120 reduce disease severity in mouse models of UC and CD

Fig. 5.1 Histopathological severity in UC

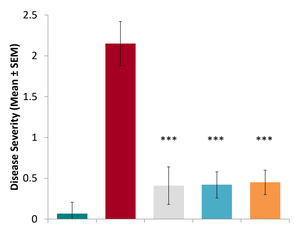


Fig. 5.2 Histopathological severity in CD

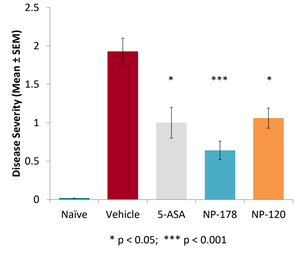
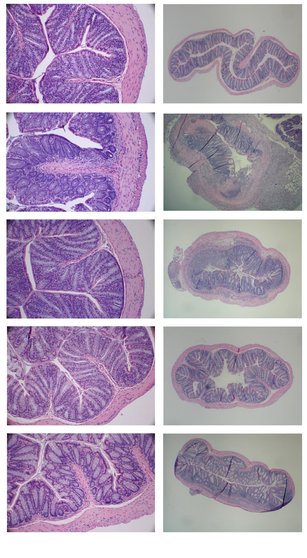


Fig. 5.3 H&E stained colon samples from mice with UC (left, 50x magnification) and CD (right, 40x); Top to bottom: Naïve, Vehicle, 5-ASA, NP-178, NP-120



- In UC, all treatments showed similar levels of reduction in histopathological disease severity.
- In CD, NP-178 showed the largest reduction in severity, followed by 5-ASA and NP-120. Differences between groups were not statistically significant.

Scoring

Table 1. Disease Activity Index

Score	Weight Loss (%)	Stool Consistency	Occult/Gross Bleeding
0	No Loss	Normal	Normal
1	1 – 5		
2	5 – 10	Loose	Occult
3	10 – 15		
4	> 15	Diarrhea	Gross Bleeding

Table 2. Histopathology

Score	Observation
0	No sign inflammation
1	Very low level of inflammation
2	Low level of leukocytic infiltration, low level of inflammation
3	High level of leukocytic infiltration, high vascular density, inflammation and thickening of colon wall
4	Transmural infiltration, loss of goblet cells, high vascular density, crypt abscesses, thickening of colon wall and ulceration

Conclusions & Future Work

- Experiments in murine models of IBD validated the drug-repurposing approach.
- NP-178 and NP-120 reduced the disease activity index, improved survival, and reduced inflammation and disease severity in both the oxazolone-induced colitis model and the TNBS-induced Crohn's Disease model.
- In both models, NP-178 and NP-120 had similar of better efficacy than 5-ASA, the frontline treatment in IBD.
- The mechanism of action is under investigation.
- A phase II clinical trial in ulcerative colitis with NP-178 is planned with enrolment expected to begin in fall 2019.

References

1) Boirivant M, Fuss IJ, Chu A, Strober W. Oxazolone Colitis: A Murine Model of T Helper Cell Type 2 Colitis Treatable of Antibodies of Interleukin 4. J Exp Med 1998;188(10):1929-39.

2) Neurath MF, Fuss I, Kelsall BL, Stüber E, Strober W. Antibodies to Interleukin 12 abrogate established experimental colitis in mice. J Exp Med 1995;182(5):1281-90.

Disclosures

- Algernon Pharmaceuticals designed and funded this study. Mark Williams is an employee of Algernon Pharmaceuticals.

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